

UC Davis

UC Davis Previously Published Works

Title

Fragile X Syndrome and Fetal Alcohol Syndrome: Occurrence of Dual Diagnosis in a Set of Triplets

Permalink

<https://escholarship.org/uc/item/7232z4pj>

Journal

Journal of Developmental and Behavioral Pediatrics, 44(7)

ISSN

0196-206X

Authors

Aishworiya, Ramkumar
Biag, Hazel Maridith Barlahan
Salcedo-Arellano, Maria Jimena
[et al.](#)

Publication Date

2023-08-08

DOI

10.1097/dbp.0000000000001204

Peer reviewed



HHS Public Access

Author manuscript

J Dev Behav Pediatr. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

J Dev Behav Pediatr. 2023 September 01; 44(7): e470–e475. doi:10.1097/DBP.0000000000001204.

Fragile X Syndrome and Fetal Alcohol Syndrome - occurrence of dual diagnosis in a set of triplets

Ramkumar Aishworiya, MMed^{1,2,3}, Hazel Maridith Barlahan Biag, MD^{1,4}, Maria Jimena Salcedo-Arellano, MD^{1,4}, Zayan Musa, BS^{1,4}, Andrea Schneider, PhD^{1,4}, Courtney Clark, BS^{1,4}, Ellery Santos, MD^{1,4}, Flora Tassone, PhD^{1,5}, Randi Hagerman, MD^{1,4}

¹Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California Davis, California, United States of America.

²Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore.

³Department of Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

⁴Department of Pediatrics, University of California Davis School of Medicine, Sacramento, California, United States of America.

⁵Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, Sacramento, California, United States of America.

Abstract

Background: Fragile X syndrome (FXS) and Fetal Alcohol syndrome (FAS) disorders are both common causes of intellectual disability in children. When both conditions are present in the same individual, the resultant phenotype may make identification of clinical issues and management challenging.

Case Presentation: In this case report, we present a case of triplets who had significant in-utero alcohol exposure; two of whom also have FXS and the other not having the Fragile X mutation.

Corresponding Author: Dr Ramkumar Aishworiya, Fellow, International Training Program in Neurodevelopmental Disorders, MIND Institute, UC Davis Health System, 2825 50th Street, Sacramento, CA 95817, paearam@nus.edu.sg, Phone: (916) 703-0247, Fax (916) 703-0240, Consultant Khoo Teck Puat – National University Children's Medical Institute, National University Health System, 5 Lower Kent Ridge Road, Singapore 119074, paearam@nus.edu.sg, Phone: +65-67795555, Fax: +65-68724130.

Contributors Statement: All authors contributed to the study conception and design. Material preparation was performed by Ramkumar Aishworiya, Hazel Maridith Barlahan Biag, Maria Jimena Salcedo-Arellano, Randi Hagerman and Zayan Musa, data collection were performed by Ramkumar Aishworiya, Hazel Maridith Barlahan Biag, Maria Jimena Salcedo-Arellano, Andrea Schneider, Courtney Clark, Ellery Santos, Randi Hagerman and Flora Tassone. The first draft of the manuscript was written by Ramkumar Aishworiya and all authors commented on and critically contributed to previous versions of the manuscript. All authors read and approved the final manuscript.

Statements and Declarations

Ethics approval: Written informed consent was obtained from legal guardian of the individuals with full agreement for the publishing of their clinical details, evaluation findings and photograph in a journal article.

Data access: Not Applicable

Data sharing statement: Not Applicable

Previous presentation of the information reported in the manuscript: Nil

Conflicts of interest: The authors have indicated that they have no conflicts of interest to declare that are relevant to the content of this article.

The siblings with FXS have subtle differences in physical phenotype compared to the other one, who has prominent features of partial fetal alcohol syndrome instead. However, all 3 siblings have intellectual impairment (although this is more severe in the two with FXS), meet diagnostic criteria for autism spectrum disorder and present with severe behavioral challenges. The clinical presentation of the two siblings with FXS is much more severe as compared to a child with FXS alone and this is likely due to the additive effect of in-utero alcohol exposure and environmental factors. We discuss the combination of these two pathologies and how this can affect the overall clinical presentation.

Conclusion: In the management of children with FXS, evaluation for other risk-factors that can have neurobehavioral sequelae is important and these can impact clinical presentation and prognosis.

Keywords

Fragile X syndrome; Fetal alcohol spectrum disorder; in-utero alcohol exposure; challenging behaviors

INTRODUCTION

Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by the silencing of the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene due to presence of > 200 CGG repeats resulting in loss of the *FMR1* protein (FMRP).¹ Approximately 1 in 8,000 females and 1 in 5,000 males in the United States (US) have the full *FMR1* gene mutation.^{2, 3} FMRP is an RNA binding protein that carries out key roles in mRNA translation, synaptic connectivity, RNA stability and ion channel transport regulation.^{4, 5} Lower levels of FMRP in individuals with FXS account for the developmental challenges encountered by individuals with the syndrome. FXS is the most common inheritable monogenic cause of autism spectrum disorders (ASD) and intellectual disability (ID).⁶ Individuals with FXS show a wide range of phenotypic traits including prominent ears, above-average head circumference/macrocephaly, hyper-extensible finger joints, and an elongated face. Behavior and cognitive difficulties may include language delays, aggression, anxiety, impulsivity, and hyperactivity.⁷ Due to its X-linked inheritance pattern, mothers of boys with FXS have either the full mutation or the premutation (PM; 55 – 200 CGG repeats), both associated with several medical conditions.⁸ The PM state for example is associated with fragile X-associated primary ovarian insufficiency (FXPOI),^{9, 10} and fragile X-associated tremor ataxia syndrome (FXTAS).¹¹ Further, fragile X-associated neuropsychiatric disorders (FXAND)¹² which includes conditions like anxiety, attention deficit hyperactivity disorder (ADHD), phobias and obsessive compulsive disorders are also associated with the PM state. The pathophysiology of these conditions is attributed to the RNA toxicity caused by elevated levels of *FMR1* mRNA in PM individuals.¹³

Fetal Alcohol Spectrum Disorders (FASD) represent a collective entity of disorders including fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorders (ARND) and alcohol-related birth defects (ARBD), that manifest with developmental and neurological impairments in individuals with a history of in-utero alcohol exposure.^{14, 15} FASD/FAS are among the most common nonheritable

causes of ID.¹⁶ The prevalence of FAS is estimated to be between 0.3 and 0.8 per 1,000 children in US, while the prevalence of FASD is approximately 33.5 per 1,000. The cognitive and behavioural impairments associated with FASD reflect underlying functional or structural changes in the brain.¹⁷ Patients can present with a reduced overall brain size, or with disproportionate reductions in the size of specific brain structures including the basal ganglia, the cerebellum and the corpus callosum,^{17–19} and/or temporal lobe asymmetry; causing impairments in development, memory and other cognitive processes. Characteristic features of FASD/FAS include facial dysmorphic features, smooth philtrum, microcephaly and growth retardation.¹⁴ In addition, cognitive deficits, learning difficulties, attention deficits and hyperactivity are commonly seen.²⁰ The percentage of women who consume alcohol during pregnancy has increased in recent years in the general population,^{21, 22} and carriers of the *FMR1* PM have an increased likelihood for alcohol and substance abuse throughout their lifespan, with several case reports of carriers having alcohol addiction.^{23, 24} The greater prevalence of neuropsychiatric disorders including ADHD may contribute to the propensity for alcohol intake in *FMR1* PM carriers.^{12, 25} Despite the increased risk for alcohol consumption among PM carriers, there is limited literature currently about children who have both FXS and FASD, highlighting the need for further research in this entity.

In this case report, we present a case of 6-year-old triplets. Two are identical twins with FXS (triplet 1 and 2) and one is a fraternal triplet (triplet 3) who does not have the fragile X mutation. The triplets had significant alcohol exposure in-utero due to chronic alcoholism in their mother who is an *FMR1* PM carrier. Although the triplets had similar in-utero alcohol exposure, the fraternal triplet without the fragile X mutation shows characteristic facial features consistent with partial FAS – thin vermilion border of the upper lip, smooth philtrum and upturned nose, unlike the other two who have features of FXS. We discuss the clinical, behavioral and cognitive features of the triplets and compare and contrast their presentation.

METHODS

The individuals reported in this case report were seen at a Fragile X Research and Treatment Center in a tertiary academic institution. Informed signed consent was obtained from their adoptive mother (who has legal guardianship of all the children) for submission of this manuscript with their clinical details, evaluation findings and photograph. Evaluation included clinical history and physical examination by a developmental-behavioral pediatrician, standardized neuropsychological testing by a qualified psychologist (for cognitive skills using the Leiter non-verbal scale as well as for the presence of autism spectrum disorder using the Autism Diagnostic Observation Schedule 2nd Edition, ADOS-2) and parent-completed standardized questionnaires (using the Aberrant Behavior Checklist and the Vineland Adaptive Behavior Scaled to assess challenging behaviors and adaptive skills respectively). Molecular analysis included DNA testing for the *FMR1* mutations by Southern Blot and PCR carried out on genomic DNA isolated from whole blood.^{26, 27}

Case details

The triplets are currently under the care of their adoptive parents, who took them in when they were 3 years of age. Details of their perinatal and birth history are minimal, but it is known that there was a history of heavy alcohol and substance abuse (including cocaine and opioids) by the biological mother during pregnancy from the birth records. They were naturally conceived and born at approximately 28 weeks of gestation via caesarian section and required a few weeks stay in the neonatal intensive care unit (NICU). Triplets 1 and 2 are identical and triplet 3 is a fraternal sibling. There are no details available about their postnatal complications, but all the triplets had to wear cranial helmets in their infancy as noted from a photograph of them at a few months of age. They were not breast fed after birth and were removed from their biological mother's care at 3 months of age (exact reason unknown). While information on their early childhood years is minimal, it is known that all 3 of them were placed together in two separate foster homes consecutively during their 1st 3 years of life; these were not kinship homes. In one of those placements the triplets experienced additional exposure to substance abuse and neglect, with reports of excessive restraint in their strollers due to significant hyperactivity.

Currently, the triplets are in their 3rd foster home and have since been adopted within this family. They attend school and receive speech and language therapy, occupational therapy and applied behavior analysis (ABA) therapy. Their physical examination findings and their cognitive and behavior evaluations are shown in Table 1. Figure 1 shows a comparative photo of the triplets standing next to each other (from left to right: Triplet 1, Triplet 3, Triplet 2).

Triplet 1.

Triplet 1 was diagnosed with FXS when he was 2.5 years of age and ASD when he was 6 years old. He was also diagnosed with attention deficit hyperactivity disorder (ADHD) at 6 years of age. His birth weight was 3 pounds and 6 ounces. When he was taken into the care of his current adoptive parent at 3 years of age, he was minimally verbal and had limited social communication. He has had a grommet tube inserted in both his ears for recurrent ear infections but does not have any other chronic medical illnesses. His current behavioral phenotype includes limited language skills and aggressive behavior such as kicking, pinching and hitting others, and self-injurious behavior including head banging. He is also hyperactive and has difficulties with sustained attention. He is not yet toilet trained but has some awareness of bladder and bowel movements. He does not have difficulties with sleep on his current medications; he tends to eat rapidly and overstuff his mouth. His current medications include clonidine given for sleep, sertraline for anxiety, trazodone for sleep, risperidone for aggression, metformin as a targeted treatment for FXS and methylphenidate for his ADHD. DNA testing for FXS indicates that he is a full mutation size mosaic, with *FMR1* alleles >200 CGG repeats and an allele where the CGG repeat was deleted. Results of psychological evaluation indicated ASD with severity scores in the high range, ID and adaptive behavior skills in the extremely low range.

Triplet 2.

Triplet 2 was diagnosed with FXS at 2.5 years of age and ASD and ADHD when he was 6 years old. His birth weight was 3 pounds and 15 ounces. When he was taken into the care of his current foster parents at 3 years of age, his verbal and social abilities were similar to triplet 1. He has had a surgery for inguinal hernia at 3 years of age but apart from this, does not have any chronic medical illnesses. Currently, his main challenges are aggressive behavior, developmental delay, and delayed social communication skills. His aggressive behaviors include head banging, biting himself and others, and throwing things when he does not get his way. Hyperactivity and inattention are also a major concern, and he has low frustration tolerance. He is described as friendlier compared to his other triplet siblings. Triplet 2 uses mainly phrase-level speech and tends to have repetitive speech. He also has stereotypic behaviors including hand flapping and rocking. He is toilet trained during the day but not yet at night. Like triplet 1, he tends to eat rapidly and is reported to be very anxious, especially when separated from his adoptive mother. His current medications include clonidine for sleep, trazodone for sleep, risperidone for aggression, metformin as a targeted treatment for FXS, and methylphenidate for his ADHD. Like his identical twin (triplet 1), DNA testing for FXS showed that he is a full mutation size mosaic, with *FMR1* alleles >200 CGG repeats and an allele where the CGG repeat was deleted. Again, similar to triplet 1, psychological evaluation indicated ASD with severity scores in the high range, ID and adaptive behavior skills in the extremely low range.

Triplet 3.

Triplet 3 has a normal *FMR1* allele (30 CGG repeats) with a diagnosis of ASD and PFAS per clinical evaluation; when he was 6 years of age. He had hyperactivity but did not meet diagnostic criteria for ADHD. His birth weight was 2 pounds so he was smaller in weight compared to his other 2 triplet siblings and was the last to be discharged from the NICU. At 3 years of age, he could only speak in single words. He was of very small build and was a picky eater. Over the past 3 years, he has not had any hospitalizations or chronic medical illnesses. He continues to be a selective eater and is of a small build with height and weight both being less than the 3rd percentile. (Table 1). Triplet 3 also has a smooth philtrum and thin vermilion border, and together with his growth parameters, met the diagnostic criteria for PFAS. He is not yet toilet trained although he has some awareness of his bowel movements. His main challenges include developmental delay, social communication, and aggressive behavior. He is currently able to speak in phrases and can hold a simple conversation but tends to have repetitive speech. He has difficulty with transitions and has frequent 'meltdowns' in behavior. These manifest as head banging, hitting himself and those around him, and biting those around him. He does not bite himself. He has poor eye contact and is very hyperactive in general. Compared to his other 2 triplet siblings, Triplet 3 is better at learning and picks up new information more quickly. He is described to be more 'devious' compared to the other 2 and often plays pranks on his brothers. He is also moodier and more anxious compared to his brothers. Triplet 3 tends to sleep for shorter durations and is often awake in the early morning hours. His current medications include clonidine for sleep, trazodone to help with sleep problems and guanfacine to calm him down in terms of his hyperactivity. Psychological testing showed the presence of ASD with severity scores in the

mild range, cognitive ability in the below average range and adaptive skills in the extremely low range.

DISCUSSION

In this study we report on the physical and clinical phenotype of a set of triplets, two with FXS and one without, who were affected to varying degrees by FASD. The physical exam shows similar height for age (< 5 percentile, likely driven in combination by FASD and early childhood neglect); however, the sibling without FXS has a smaller head circumference and weight (<5 percentile) compared to the other two. Ears were found to be longer and more prominent only in the 2 siblings with FXS, who also had greater testicular volume, hyperextensible joints and double-jointed thumbs as expected from the FXS phenotype. None of the triplets have microcephaly or seizure disorders, needed to fulfill clinical criteria for FAS, nor had any additional ARBD. Although all the triplets had equal in-utero exposure to alcohol, the triplet without the Fragile X mutation has more characteristic physical phenotypic features derived from alcohol exposure. So, the full Fragile X mutation could have buffered the presence of the physical features of FASD. Interestingly, both triplets with FXS were mosaic for the presence of a full mutation allele and a deleted allele, meaning an allele without the CGG expansion. The deleted allele could produce some FMRP, and this could moderate the clinical phenotype, although a previous case series of such cases did not consistently show a less severe phenotype.²⁸ Therefore, it may be more difficult to evaluate for typical features of FASD in the presence of FXS as seen here.

The twins who have FXS have a more severe presentation of neurobehavioral disabilities compared to the other triplet, with lower non-verbal IQ scores and a higher ADOS-2 comparison score reflecting weaker cognitive skills with more ASD-related symptoms. They also had more aggressive and challenging behaviors and ADHD. Both of these likely reflect the implications of the presence of FXS in addition to the effect of in-utero alcohol exposure. The twins' extremely challenging behaviors which are much more severe compared to those seen in the typical child with FXS could reflect the synergistic effect of the *FMR1* fully methylated mutation, the in-utero alcohol exposure and the history of abuse and neglect in early life. Although the twins with FXS fall short for a FASD diagnosis based on clinical findings, the fraternal sibling meets all criteria for PFAS with behavioral impairment, with mild cognitive impairment. For a complete evaluation of FAS, in the absence of microcephaly or seizures, brain imaging is required to rule out structural brain abnormalities, unavailable at the time of clinical assessment. Since, we propose a PFAS diagnosis that could potentially change to FAS with further evaluation. Of note, diagnosis of concomitant PFAS in the identical twins is challenging since the physical features of FASD are likely masked/buffered by the physical features of FXS. It is also important to note that in the case of these triplets, prematurity is also an important underlying risk factor for the presence of slower growth and developmental delays. Triplet 3 is also a fraternal sibling to the other two triplets and this implies greater genetic variation, which could also be contributory to the varying clinical presentation of this triplet. Further, marked environmental adverse factors in early childhood including unstable caregiver arrangements, possible neglect and exposure to substance abuse could all have contributed to the overall presentation with challenging behaviors and developmental delays. These adverse childhood

experiences make it harder to tease out the precise reason for each clinical phenotype and it is likely that there is a complex interplay among the various factors.

CONCLUSION

In this case report, we highlight the differing effects due to the presence of the full Fragile X mutation in terms of physical and cognitive profile in a set of triplets with equal in-utero alcohol exposure. The presence of dual pathologies in the same child is possible and can lead to a more severe clinical presentation. It is important to evaluate for the presence of other possible risk factors for neuro-behavioral sequelae in children with FXS, such as alcohol and illicit substance exposure during pregnancy. In-utero exposure to alcohol is a crucial factor that, in this case, has had profound effects on the neuro-behavioral phenotype, especially in terms of severe externalizing behavior in all the triplets. Conversely, in children who present with known in-utero alcohol exposure and related sequelae, it is still pertinent to include a detailed family history and consider genetic testing to identify concomitant genetic conditions like FXS. Awareness of the presence of risk factors such as in-utero alcohol exposure can guide clinical management with implications for eventual outcome.

Sources of Funding:

This research was supported by grants from NICHD including HD036071 and the MIND Institute Intellectual and Developmental Disabilities Research Center P50 HD103526. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Hagerman RJ, Berry-Kravis E, Hazlett HC, et al. Fragile X syndrome. *Nat Rev Dis Primers*. 2017;3:17065. [PubMed: 28960184]
2. Bagni C, Tassone F, Neri G et al. Fragile X syndrome: causes, diagnosis, mechanisms, and therapeutics. *J Clin Invest*. 2012;122(12):4314–4322. [PubMed: 23202739]
3. Protic DD, Aishworiya R, Salcedo-Arellano MJ, et al. Fragile X Syndrome: From Molecular Aspect to Clinical Treatment. *Int J Mol Sci*. 2022;23(4).
4. Salcedo-Arellano MJ, Hagerman RJ, Martinez-Cerdeno V. Fragile X syndrome: clinical presentation, pathology and treatment. *Gac Med Mex*. 2020;156(1):60–66. [PubMed: 32026885]
5. Irwin SA, Galvez R, Greenough WT. Dendritic spine structural anomalies in fragile-X mental retardation syndrome. *Cereb Cortex*. 2000;10(10):1038–1044. [PubMed: 11007554]
6. Maia N, Nabais Sá MJ, Melo-Pires M, et al. Intellectual disability genomics: current state, pitfalls and future challenges. *BMC Genomics*. 2021;22(1):909. [PubMed: 34930158]
7. Kidd SA, Lachiewicz A, Barbouth D, et al. Fragile X syndrome: a review of associated medical problems. *Pediatrics*. 2014;134(5):995–1005. [PubMed: 25287458]
8. Hagerman RJH PJ Fragile X Syndrome and Premutation Disorders. London: Mac Keith Press; 2020.
9. Cronister A, Schreiner R, Wittenberger M, et al. Heterozygous fragile X female: historical, physical, cognitive, and cytogenetic features. *Am J Med Genet*. 1991;38(2–3):269–274. [PubMed: 2018071]
10. Sullivan AK, Marcus M, Epstein MP, et al. Association of FMR1 repeat size with ovarian dysfunction. *Hum Reprod*. 2005;20(2):402–412. [PubMed: 15608041]
11. Hagerman RJ, Hagerman P. Fragile X-associated tremor/ataxia syndrome - features, mechanisms and management. *Nat Rev Neurol*. 2016;12(7):403–412. [PubMed: 27340021]
12. Hagerman RJ, Protic D, Rajaratnam A, et al. Fragile X-Associated Neuropsychiatric Disorders (FXAND). *Front Psychiatry*. 2018;9:564. [PubMed: 30483160]

13. Tassone F, Hagerman RJ, Taylor AK, et al. Elevated levels of FMR1 mRNA in carrier males: a new mechanism of involvement in the fragile-X syndrome. *Am J Hum Genet.* 2000;66(1):6–15. [PubMed: 10631132]
14. Stratton K, Howe C, Battaglia FC. *Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment*: National Academies Press; 1996.
15. Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. *Pediatrics.* 2016;138(2).
16. Denny L, Coles S, Blitz R. Fetal Alcohol Syndrome and Fetal Alcohol Spectrum Disorders. *Am Fam Physician.* 2017;96(8):515–522. [PubMed: 29094891]
17. Roebuck TM, Mattson SN, Riley EP. A review of the neuroanatomical findings in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcoholism: Clinical and Experimental Research.* 1998;22(2):339–344. [PubMed: 9581638]
18. Mattson SN, Riley EP, Sowell ER, et al. A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research.* 1996;20(6):1088–1093. [PubMed: 8892532]
19. Riley EP, Mattson SN, Sowell ER, et al. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcoholism: Clinical and Experimental Research.* 1995;19(5):1198–1202. [PubMed: 8561290]
20. Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcoholism: Clinical and experimental research.* 1998.
21. England LJ, Bennett C, Denny CH, et al. Alcohol use and co-use of other substances among pregnant females aged 12–44 years—United States, 2015–2018. *Morbidity and Mortality Weekly Report.* 2020;69(31):1009. [PubMed: 32759915]
22. Tan CH, Denny CH, Cheal NE, et al. Alcohol use and binge drinking among women of childbearing age—United States, 2011–2013. *Morbidity and Mortality Weekly Report.* 2015;64(37):1042–1046. [PubMed: 26401713]
23. Dorn MB, Mazzocco MM, Hagerman RJ. Behavioral and psychiatric disorders in adult male carriers of fragile X. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1994;33(2):256–264. [PubMed: 8150798]
24. Schneider A, Seritan A, Tassone F, et al. Psychiatric features in high-functioning adult brothers with fragile x spectrum disorders. *Prim Care Companion CNS Disord.* 2013;15(2).
25. Farzin F, Perry H, Hessel D, et al. Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *Journal of developmental and behavioral pediatrics : JDBP.* 2006;27(2 Suppl):S137–144. [PubMed: 16685180]
26. Tassone F, Pan R, Amiri K, et al. A rapid polymerase chain reaction-based screening method for identification of all expanded alleles of the fragile X (FMR1) gene in newborn and high-risk populations. *J Mol Diagn.* 2008;10(1):43–49. [PubMed: 18165273]
27. Filipovic-Sadic S, Sah S, Chen L, et al. A novel *FMR1* PCR method for the routine detection of low abundance expanded alleles and full mutations in fragile X syndrome. *Clinical chemistry.* 2010;56(3):399–408. [PubMed: 20056738]
28. Jiraanont P, Kumar M, Tang H-T, et al. Size and methylation mosaicism in males with Fragile X syndrome. *Expert review of molecular diagnostics.* 2017;17(11):1023–1032. [PubMed: 28929824]
29. Aman MG, Norris M, Kaat AJ, Andrews H, Choo T-H, Chen C, Wheeler A, Bann C, Erickson C. Factor Structure of the Aberrant Behavior Checklist in Individuals with Fragile X Syndrome: Clarifications and Future Guidance. *Journal of Child and Adolescent Psychopharmacology.* 2020; 30(8): 512–521. [PubMed: 32746626]



Figure 1:
Photograph of the Triplets, from left to right: Triple 1, Triplet 3, Triplet 2 (Triplet 3 is the one without FXS)

Table 1:

Summary of neuropsychiatric evaluations and clinical examination findings

Measure/Assessment	Triplet 1	Triplet 2	Triplet 3
Leiter-3 Non-Verbal IQ	61	55	84
Social Affect	13	9	3
Restricted and Repetitive Behavior	7	7	5
ADOS-2 ^a			
ADOS-2 total score	20	15	8
Comparison Score	8	7	4
Overall Diagnosis	ASD	ASD	ASD
Severity level	High	High	Low
ABC-C ^b			
Irritability	38 (>90 th)	39 (>90 th)	36 (>90 th)
Socially unresponsive	4 (>25 th)	5 (50 th)	3 (>25 th)
Stereotypy	10 (>75 th)	10 (>75 th)	12 (>75 th)
Hyperactivity	37 (>99 th)	43 (>99 th)	37 (>99 th)
Inappropriate Speech	4 (50 th)	7 (75 th)	6 (>50 th)
VABS-2 ^c			
Communication	62	60	62
Daily Living Skills	72	71	64
Socialization	48	50	48
Adaptive Behavior Composite	62	61	59
Clinical Features[*]			
Weight in kilograms (percentile %)	17.35 (25)	18.35 (50)	15.4 (< 3)
Height in centimeters (percentile %)	106.9 (< 3)	105.2 (< 3)	101.2 (< 3)
Occipital-frontal circumference (cm)	51.2 (75)	51 (75)	50 (50)
Ear length in cm (SD) ^d	5.8 (+2)	5.6 (+1)	5.0 (-2)
Ear width in cm (SD)	3.7 (-1)	4.0 (+1)	2.5 (> -2SD)
Outer ear prominence in cm	2.5	2.3	1.5
Inner canthal distance in cm (SD)	2.9 (+1)	3.0 (+1)	3.2 (+2)
Outer canthal distance in cm (SD)	8.0 (mean)	8.2 (+1)	8.3 (+1)
Facial features	Intact philtrum, absent epicanthal folds, broad and wide palate, slight clinodactyly of 5 th right finger	Intact philtrum, absent epicanthal folds, broad and wide palate	Flat and broad philtrum with thin lips, absent epicanthal folds, broad palate, slight clinodactyly in 5 th finger bilaterally
Flexion at the MCP joint	Well over 90 degrees	Well over 90 degrees	Not hyperextensible
Thumb joint	Double- jointed	Double- jointed	Not double-jointed
Testicular volume	4 ml	4 ml	2 ml
Others	Widened space between 1 st and 2 nd toe bilaterally; complete flat feet bilaterally	Widened space between 1 st and 2 nd toe bilaterally; relatively flat feet with slight arch in right foot	Widened space between 1 st and 2 nd toe bilaterally; complete flat feet bilaterally

Measure/Assessment	Triplet 1	Triplet 2	Triplet 3
Co-Morbidities	ASD ^e , ADHD ^f , Sleep Disturbance, Anxiety, Aggression	ASD, ADHD, Sleep Disturbance, Aggression	FASD ^g , ASD, Sleep Disturbance, Hyperactivity

Notes:

* Clinical evaluations were done at age of 6 years and 5 months and neuropsychiatric evaluations at 6 years and 1 month of age.

^aAutism Diagnostic Observation Schedule

^bAberrant Behavior Checklist – Community; percentiles according to Aman et al 2020 (reference number 29)

^cVineland Adaptive Behavior Scales

^dStandard Deviation(s) above or below mean

^eAutism Spectrum Disorder

^fAttention Deficit Hyperactivity Disorder

^gFetal Alcohol Spectrum Disorders

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript