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Consanguinity and Associated Conditions Prevalence in Fragile X Syndrome Cases in Eastern Region in Saudi Arabia

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Abstract
Fragile X Syndrome (FXS) is an X-linked genetic defect and the leading monogenic cause of inheritable Intellectual Disability (ID), which is caused by an abnormal expansion in trinucleotides CCG repeats in the Fragile X Mental Retardation 1 (FMR1) gene. Consanguinity has been reported to involve a high risk of inheriting this genetic disorder, while consanguineous marriage in Saudi Arabia is estaimated at 56%. This study aimed to examine the relationship between the FXS prevalence, the prevalence of the FXS associated conditions, and parental consanguinity in the FXS patients in the Eastern Region in Saudi Arabia. We examined 17 patients with positive alteration in FMR1 gene in hospitals in Dammam and Dhahran districts by extracting data from the patients' medical records. The study variables were as follows: level of ID, FXS associated conditions, parental consanguinity, and the number of FXS siblings in the family. We used descriptive statistics to characterize the case relations, and prevalence was expressed in percentages.Data on patients were described in gender (16 males, 1 female), and age was distributed from 1-21 in five aged range categories. 15 cases with FXS and two premutations with ID and associated conditions frequency resulted. The two were excluded from ID and associated condition frequency, along with the female patient with FXS who had no associated condition. Consanguinity was found in 13/17 cases (76.47%), in which 2 cases were premutations, and 7 out of nine families included in this study were consanguineous, with four families having FXS siblings. The associated conditions were found in 14 FXS cases; four cases were observed with hyperactivity (26.57%), two cases with ASD, two with speech delay, two cases with aggressive behavior (14.3%), and one case with Hypertonia, abnormal laughter, epilepsy, and reckless behavior (7.14%). The results of this study suggest a high effect of consanguineous parenting on FXS prevalence. The test for associated conditions showed direct relation with increasing rates in FXS male cases. These findings contradicted with the results of previous studies in Saudi Arabia and other studies around the world. Preselection-based patients on positive cytogenetic test result are likely to have effected the results of this study. Also, the results may be affected by the small number of study participants.
Keywords: key words, orkforce sizing, job-shop production, holonic model

1. Introduction

Intellectual Disability (ID) prevalence in developed countries is estimated at 2-3%, although prevalence of mild level of ID is very widely spread [Leonard and Wen, 2002]. In a recent estimation, X-linked genetic defects were associated with 10% of males with severe ID [Ropers and Hamel, 2005]. Fragile X Syndrome (FXS) is a X-lined syndrome and the leading monogenic cause of inheritable ID that passes from the parent to the child in an unusual inheritance pattern, showing increased frequently as the mutant gene passes to subsequent generations (the Sherman paradox) [Hagerman, 2002; Sherman *et al.*, 1985]. FXS is characterized by mild to severe ID levels, which are accompanied by macroorchidism established around puberty in males and distinct facial morphology (long face, large and protruded ears) [Hagerman and Hagerman, 2002]. It is more severe in males than in females, with prevalence one in 4000–6000 males and 1 in 7000–10,000 females [Mandel and Biancalana, 2004]. Males are generally unable to live independently, while females may live independently with some learning difficulties. Also, the physical features in female are tender [Pembrey *et al.*, 2001]. FXS is almost exclusively caused by an abnormal expansion in the number of the trinucleotides CGG repeats located in the 5' UTR (untranslated region) in Fragile X mental retardation 1 (*FMR1*) gene at Xq27.3 near the end of the long arm. The number of CGG repeats determine whether the individual has a normal allele (less than 55 repeats), premutations (approximately 55–200 repeats), or a full mutation or FXS (more than 200 repeats). In most FXS individuals, the CGG repeats are massively expanded and hyper methylated, which result in the silence of the FMR1 gene and a deficiency of the fragile mantel retardation protein (FMRP), and thus FXS [Kunst and Warren, 1994; Snow *et al.*, 1993]. Premutation individuals typically have normal FMRP levels; however, some have lower FMRP levels. As a result, they may have mild to moderate ID, behavioral and health conditions associated with FXS, and, in some cases, mild versions of the physical features seen in FXS [Hagerman *et al.*, 2001; Hagerman, 2002; Jacquemont *et al.*, 2003].

The variations in the FMR1 gene have been linked with a number of associated conditions including attention problems, hyperactivity, aggressiveness, Autism Spectrum Disorder (ASD), seizures, and depression. [Loesch *et al.*, 2007; Sullivan *et al.*, 2006].

High prevalence of birth defects and ID are often associated with consanguinity rates [Bittles, 2003; 2005]. A plausible explanation is that consanguinity is associated with a higher risk for recessive disorders [Pouya *et al.*, 2009]. In Saudi Arabia, consanguineous marriage rates are up to 56% [El-Mouzan *et al.*, 2007]. Several studies have assessed the prevalence of FXS in cohort groups, e.g. China [Chen *et al.*, 2015], Kuwait [Bastaki *et al.*, 2004], Turkey [Demirhan *et al.*, 2003], and Saudi Arabia [Al Husain *et al.*, 2000]. However, studies on the relationship between parental consanguinity and FXS are scarce [Pouya *et al.*, 2009]. Since FXS has unusual inheritance pattern increasing frequently in every subsequent generation, this study aimed to determine the relationship between the FXS prevalence and parental consanguinity in the FXS patients in several hospitals in the Eastern Region in Saudi Arabia. In addition, this study attempted to discover the prevalence of the FXS associated conditions in these patients.

2. Method

Patients tested positive for the alteration in FMR1 gene in the pediatric clinics in hospitals in Dammam and Dhahran districts, which are considered as the biggest hospitals in the Eastern Region in Saudi Arabia, were involved in this study. Participants were selected based on the mine physician diagnosis and screening for FXS by cytogenetic methods. The study variables were as follows: level of ID, FXS associated conditions, parental consanguinity, and the number of FXS siblings in the family. Data were extracted from the patients' medical records with the coordination of the patients' main physician. The extracted data were recorded in collecting sheet.

Data were numerically coded and transferred to the Statistical Package for Social Science (SPSS) (Chicago, IL, USA) pack 22. Descriptive statistics were used to characterize the prevalence of parents' consanguinity and associated conditions. Prevalence was expressed as a percentage.

3. Results

The study included 17 cases with FMR1 mutation; 16 males and one female, whose ages ranged from 1 to 21 years (mean, 9.24) (Table 1). 15 cases were FXS and two premutations with ID and associated condition present in FXS. The two premutation males were excluded from ID level and associated conditions frequency. The FXS female has no associated condition; therefore she was excluded from associated conditions frequency.

The majority of ID level is the mild group 6/15 (40%), followed by the moderate group 5/15 (33.33%), and 4/15 (26.66%) in the severe group patients.

TABLE 1. Age distribution of 17 patients positive for alteration in FMR1 gene (Males=16; Females=1).

Age	No. of Males	%	No. of Females	%
0-5	7	43.75	-	-
6-10	3	18.75	-	-
11-15	3	18.75	1	100%
16-20	2	12.5	-	-
>20	1	6.25	-	-

Consanguinity was found in 13/17 cases (76.47%), in which 2 cases were premutations (table 2). ID, ASD, epilepsy, and hyperactivity were present in family history in 6 cases (35.29%). A total of nine families were included in this study; four families had more than one sibling of FXS in their children. Consanguineous parents were in three families, and one family had non-consanguineous parents. As shown in (table 3), most the FXS sibling were males. In the remaining five families, one family had first cousin's parents; among their two males children, one FXS and the other was normal. The rest four families had only one child.

TABLE 2. Consanguinity and ID levels in FXS and premutation cases

Feature	No. of Full FXS	Percentage	No. of premutation	Percentage
Consanguinity	11/15	73.33	2/2	100
Family history of ID	1/15	6.66	1/2	50
ID levels				
Mild	6/15	40	1/2	50
Moderate	5/15	33.33	1/2	50
Severe	4/15	26.66		

TABLE 3. Consanguinity in Families and FSX siblings

	Frequency	Percentage	Families with FXS siblings	No. of Family	FXS siblings	
					Males	Females
Consanguineous	7	77.78	3			
				1	3	-
				2	2	1
				3	2	-
Non-Consanguineous	2	22.22	1		4	-

Table 4 summarizes the associated conditions found in 14 FXS cases as percentages. The most common associated conditions observed were hyperactivity in 4/14 cases (28.57%), followed by ASD, speech delay, and aggressive behavior in 2/14 cases, the percentage of each was (14.3%). Hypertonia, abnormal laughter, epilepsy and reckless behavior were found in one case, the percentage of each was (7.14%).

TABLE 4. Summary of associated conditions in 14 FXS males

Associated Conditions	Frequency	Percentage
Hypertonia	1	7.14%
ASD	2	14.3%
Abnormal laughter	1	7.14%
Speech Delay	2	14.3%
Hyperactive	4	28.57%
Aggressive Behavior	2	14.3%
Epilepsy	1	7.14%
Reckless Behavior	1	7.14%

In the two premutation cases, ID level differed, as one had a mild ID level and the other one had a moderate level. Both had hyperactivity as an associated condition, in addition to epilepsy and speech delay in one and ASD in the other.

5. Discussion

FXS is the second most prevalent cause of ID after Down syndrome. Almost all cases of Down syndrome are de novo mutations, but FXS is always inherited with many individuals in the family tree, either as a full mutation or as a premutation [Saldarriaga *et al.*, 2014]. Studies on the relationship between consanguinity and genetic disorders have been reported from many parts of the world. However, there are only few reports from Saudi Arabia, [Al-Abdulkareem and Ballal, 1998; Al Hussain and Al Bunyan, 1997; El-Hazmi *et al.*, 1995]. Saudi Arabia is one of the countries that have high consanguinity prevalence, where Dammam city is the second highest rate 51.3% [El-Mouzan *et al.*, 2007,2008]. High prevalence (76.47%) of FXS individuals with consanguineous parents was found in this study. These findings are much higher than the prevalence found in a previous study (7.6%) in Saudi Arabia [Iqbal *et al.*, 2000]. A study of families with consanguineous and non-consanguineous parents conducted in Iran showed that high proportions of FXS individuals were in the offspring of non-consanguineous parents (15.3%), compared with families with consanguineous parents (3.4%) [Pouya *et al.*, 2009]. On the contrary, in the current study, consanguinity was found in seven families (77.78%), and only two families (22.22%) had non- consanguineous parents.

Research on a variety of disability conditions proposed that the primary health impairment that can result as a consequence of the associated conditions are a direct result of the primary impairment, even if they occur only in a subset of the FXS cases [Kirby, 2002]. Unlike individuals with other developmental syndromes such as Down syndrome (which may be easily recognized based on physical features), physical features in FXS vays depending on the degree of CGG repeat methylation and the production of FMRP. FXS is often recognized on the basis of behavioral characteristics rather than physical features (Hagerman 1996; Lachiewicz *et al.*, 1994; Lachiewicz *et al.*, 2000].

Eight associated conditions were found in this study. Hyperactivity (28.57%) was the most frequent conditions among FXS cases; this is similar to the results of a published study [Sullivan *et al.*, 2006]. On the contrary, a published study in Saudi Arabia indicated high prevalence of hyperactivity in FXS patients (92.3%) [Iqbal, *et al.*, 2000]. Most FXS individuals, especially males, show some levels of communication skills delay [Abbeduto & Hagerman, 1997]. Speech production is a major problem for many FXS individuals, and some of these problems are known to be specific to FXS [Schopmeyer and Lowe, 1992]. Speech delay is reported in several studies on the social-emotional features that define FXS. Most of these studies focused on school-age and adult males with FXS [Palmer *et al.*, 1988; Prouty *et al.*, 1988; Roberts *et al.*, 2005]. In this study, speech delay was found in two FXS males (14.3%) as the second frequent associated condition, along with ASD and aggressive behavior. Many studies show that some of the speech problems that are unique to FXS are typically

associated with ASD [Daneberga *et al.*, 2011]. FXS is the most commonly observed genetic cause of ASD, and studies have showed that 90% of FXS individuals show ASD type behaviors [Bailey *et al.*, 2000; Mc Devitt *et al.*, 2015]. ASD was present in two FXS individuals (14.3%) in this study, which is in the range of estimated ASD prevalence in FXS individuals (5% to 60%). ASD prevalence varied widely across studies due to differences in diagnostic methods [Clifford *et al.*, 2007; Hall *et al.*, 2008; Harris *et al.*, 2008; Kaufmann *et al.*, 2004; McDuffie *et al.*, 2010; Rogers *et al.*, 2001].

The FXS phenotype has been characterized in part by behaviors such as aggression, self-injurious behavior, reckless behavior, and so on. Several studies have reported prevalence of over a third (38%) among individuals with FXS who have severe aggressive behavior enough to have been diagnosed or treated for it [Arron *et al.*, 2011; Bailey *et al.*, 2008; Powis & Oliver 2014; Wheeler *et al.*, 2016;]. In this study, only two FXS individuals were diagnosed with aggressive behavior (14.3%). The difference in prevalence was due to the small group involved in this study.

In addition to the behavioral problems, certain medical problems, such as seizures, were suggested as more common in FXS [Hagerman, 1996]. Recurrent appearance of spontaneous seizures due to neuronal hyperactivity in the brain is known as epilepsy. Epilepsy is one of the chronic neurological disorders that affect people of all ages. [Qiu, 2008]. Two cases of epilepsy and premutation individuals were found in this study. Studies on epilepsy in individuals with FMR1 gene mutation have described a variety of seizure types occurring in about 10 to 40% of individuals with FXS [Kluger *et al.*, 1996; Musumeci *et al.*, 1988; Musumeci *et al.*, 1991; Musumeci *et al.*, 1999; Sabaratnam *et al.*, 2001; Vieregge *et al.*, 1989].

6. Conclusion

The study shows that 17 cases had alterations in the FMR1 gene (15 were FXS and two premutation). Consanguinity was in 76.47% of the cases. This high percentage of consanguinity in Dammam city may be a plausible explanation for the high frequency of consanguinity found in this study. Also, the frequency may be affected by the fact that the frequency of FXS cases increases in patients preselected based on the positive cytogenetic test result. Hyperactivity was the most frequent associated conditions 28.57%. The associated conditions with FXS prevalence may also be affected by preselection and the small number of study participants.

References

Abbeduto L, Hagerman RJ. Language and communication in fragile X syndrome. Mental Retardation and Developmental Disabilities Research Reviews. 1997; 3(4):322-313. doi:10.1002/(SICI)1098-2779(1997)3:4<313::AID-MRDD6>3.0.CO;2-O

Al Husain M, Salih MAM, Zaki OK, Al Othman L, Al Nasser MN. Clinical study of mentally retarded children with Fragile X Syndrome in Saudi Arabia. Ann Saudi Med. 2000 Jan; 20(1):19-16. PMID: 17322735

Al Hussain M, Al Bunyan M. Consanguineous marriages in a Saudi population and the effect of inbreeding on prenatal and postnatal mortality. Annals of tropical paediatrics. 1997; 17(2):160-155. PMID:9230979

Al-Abdulkareem AA, Ballal SG. Consanguineous marriage in an urban area of Saudi Arabia: rates and adverse health effects on the offspring. Journal of community health.1998 Feb; 23(1):83-75 doi:10.1023/A:1018727005707

Arron K, Oliver C, Moss J, Berg K Burbidge C. The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. Journal of Intellectual Disability Research. 2011 Oct 26;55(2):120-109. DOI: 10.1111/j.1365-2788.2010.01337.x

Bailey DB, Rapa M, Olmsted M, Holiday DB. Co-occuring conditions associated with FMR1 gene variations: Findings from a national parent survey. American Journal of Medical Genetics. 2008 Jun; 135A(16):2069-2060. PMID:18570292 doi:10.1002/ajmg.a.32439

Bailey DB, Hatton DD, Mesibov G, Ament N, Skinner M. Early development, temperament, and functional impairment in autism and Fragile X Syndrome. J. Autism Dev. Disord. 2000; 30(1):59-49. DOI: 10.1023/A:1005412111706

Bastaki LA, Hegazy F, Al-Heneidi MM, Turki N, Azab AS, Naguib KK. Fragile X syndrome: a clinico-genetic study of mentally retarded patients in Kuwait. Eastern Mediterranean health journal.2004; 10(1-2):124-116. PMID:16201716

Bittles AH. Consanguineous marriage and childhood health. Developmental Medicine & Child Neurology. 2003 Aug 1; 45(8):576-571. PMID:12882538 doi:10.1017/S001216220300104X

Bittles AH. Endogamy, consanguinity and community disease profiles. Community. Genet. 2005; vol.8 (1):20-17. DOI:10.1159/000083332

Chen X, Wang J, Xie H, Zhou W, Wu Y, Wang J, Qin J, Guo J, Gu Q, Zhang X, Ji T, Zhang Y, Xiong Z, Wang L, Wu X, Latham GJ, Jiang Y. Fragile X Syndrome screening in Chinese children with unknown intellectual developmental disorder. BMC Pediatrics. 2015;15(1):77-77 DOI: 10.1186/s12887-015-0394-8

Clifford S, Dissanayake C, Bui QM, Huggins R, Taylor AK, Loesch DZ. Autism spectrum phenotype in males and females with Fragile X full mutation and premutation. J. Autism Dev. Disord. 2007 Apr;37(4):747-738. PMID: 17031449 DOI: 10.1007/s10803-006-0205-z

Daneberga Z, Krumioa Z, Lace B, Bauze D, Lugovska R. The Fragile X Syndrome: 13 years of experience. Section B. Natural, Exact, and Applied Sciences. 2011 Jan;65(3-4):72-67. DOI:10.2478/v10046-011-0020-6

Demirhan O,Tastemir D, Diler RS, Firat S, Avci A. A cytogenetic study in 120 Turkish children with intellectual disability and characteristics of fragile X syndrome. Yonsei medical journal.2003 Aug;44(4):592-583.

Mc Devitt N, Gallagher L, Reilly RB. Autism Spectrum Disorder (ASD) and Fragile X Syndrome (FXS): Two Overlapping Disorders Reviewed through Electroencephalography—What Can be Interpreted from the Available Information? Brain Sci. 2015;5(2):117-92. PMCID: PMC4493458 doi:10.3390/brainsci5020092

El-Mouzan MI, Al-Salloum AA, Al-Herbish AS, Qurachi MM, Al-OmarAA. Regional variations in the prevalence of consanguinity in Saudi Arabia. *Saudi Med J. 2007;*28(12):1884-1881.

El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar A A. Consanguinity and major genetic disorders in Saudi children: a community-based crosssectional study. Ann Saudi Med. 2008;28(3):173-169. PMID: 18500181

El-Hazmi MA, Al-Swailem AR, WarsyAS, Al-Swailem AM, Sulaimani R, Al-Meshari, AA. Consanguinity among the Saudi Arabian population. Journal of medical genetics.1995; 32(8):626-623. Doi:10.1136/jmg.32.8.623

El-Mouzan MI, Al-Salloum AA, Al-Herbish AS, Qurachi MM, Al-Omar AA. Regional variations in the prevalence of consanguinity in Saudi Arabia. Saudi medical journal. 2007;28(12):1884-1881.

Hagerman RJ, Hagerman P. The Fragile X premutation: into the phenotypic fold. CurrOpin Genet Dev. 2002 Jun 1; 12(3):283-278. doi:10.1016/S0959-437X(02)00299-X

Hagerman RJ, Leehey M, Heinrichs W, Tassone F, Wilson R, Hills J, Grigsby J, Gage B, Hagerman PJ. Intention tremor, Parkinsonism, and generalized brain atrophy in male carriers of Fragile X. Neurology. 2001 Jul; 57(1):130-127. PMID: 11445641

Hagerman RJ. Physical and behavioral phenotype. In: Hagerman RJ, Cronister A, editors. Fragile X Syndrome: Diagnosis, Treatment and Research. Baltimore, MD: Johns Hopkins University Press; 1996. 3–87.

Hagerman RJ. The physical and behavioral phenotype. 3rd edition. The Johns Hopkins University Press; 2002. 109.

Hall SS, Lightbody AA, Reiss AL. Compulsive, self-injurious, and autistic behavior in children and adolescents with Fragile X Syndrome. Ame. J. Men. Retard. 2008 Jan; 113(1):53-44. PMID: 18173299 doi: 10.1352/0895-8017(2008)113[44: CSAABI] 2.0.CO;2.

Harris SW, Hessl D, Goodlin-Jones B, Ferranti J, Bacalman S, Barbato I, Tassone F, Hagerman PJ, Herman H, Hagerman RJ. Autism profiles of males with Fragile X Syndrome. Am. J. Ment. Retard. 2008 Nov; 113(6):438-427. DOI: 10.1352/2008.113:427-438

Iqbal MA, Sakati N, Nester M and Ozand P. Cytogenetic diagnosis of fragile X syndrome: study of 305 suspected cases in Saudi Arabia. Ann Saudi Med. 2000; 20(3-4):217-214. PMID: 17322660

Jacquemont S, Hagerman RJ, Leehey M, Grigsby J, Zhang L, Brunberg JA, Greco C, Des Portes V, Jardini T, Levine R, Berry-Kravis E, Brown WT, Schaeffer S, Kissel J, Tassone F, Hagerman PJ. Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. The American Journal of Human Genetics. 2003 Apr; 72(4):878-869. PMID:12638084 PMCID: PMC1180350 doi:10.1086/374321

Kaufmann WE, Cortell R, Kau AS, Bukelis I, Tierney E, Gray RM, Cox C, Capone GT, Stanard P. Autism spectrum disorder in Fragile X Syndrome: Communication, social interaction, and specific behaviors. Am. J. Med. Genet. 2004; 129(3):234-225. PMID:15326621 doi: 10.1002/ajmg.a.30229

Kirby RS. Co-occurrence of developmental disabilities with birth defects. Ment Retard Dev Disabil Res Re.2002 Sep 4; 8(3):187-182. doi: 10.1002/mrdd.10034

Kluger G, Bohm I, Laub MC, Waldenmaier C. Epilepsy and fragile X gene mutations. Pediatric Neurology. 1996; 15(4):360-358. doi:10.1016/S0887-8994(96)00251-2

Kunst CB, Warren ST. Cryptic and polar variation of the fragile X repeat could result in predisposing normal alleles. Cell. 1994 Jun; 77(6):861-853. doi:10.1016l0092-8674(94)90134-1

Lachiewicz AM, Dawson DV, Spiridigliozzi GA. Physical characteristics of young boys with fragile X syndrome: reasons for difficulties in making a diagnosis in young males. American journal of medical genetics. 2000 May 23; 92(4):236-229. PMID:10842286 doi:10.1002/(SICI)1096-8628(20000605)92:4<229::AID-AJMG1>3.0.CO;2-K

Lachiewicz AM, Spiridigliozzi GA, Gullion CM, Ransford SN, Rao K. Aberrant behaviors of young boys with fragile X syndrome. American Journal on Mental Retardation. 1994 Mar; 98(5):579-567.

PMID:8192902

Leonard H, Wen X. The epidemiology of mental retardation: Challenges and opportunities in the new millennium. Mental retardation and developmental disabilities research reviews. 2002; 8(3):134-117. doi:10.1002/mrdd.10031

Loesch DZ, Bui Q, Dissanayake C, Clifford S, Gould E, Clifford S, Gould E, Bulhak-Paterson D, Tassone F, Taylor AK, Hessl D, Hagerman RJ, Huggins RM. Molecular and cognitive predictors of the continuum of autistic behaviors in Fragile X. NeurosciBiobehav Rev. 2007;31(3):326-315. doi:10.1016/j.neubiorev.2006.09.007

Mandel JL, Biancalana V. Fragile X mental retardation syndrome: from pathogenesis to diagnostic issues. Growth hormone & IGF research. 2004 Jun; 14 Suppl:165-158.

McDuffie A, Abbeduto L, Lewis P, Kover S, Kim JS, Weber A, Brown WT. Autism spectrum disorder in children and adolescents with Fragile X Syndrome: Within-Syndrome differences and age-related changes. Am. J. Intell. Dev. Disabil. 2010 Jul; 115(4):326-307. PMCID: PMC2887668 doi:10.1352/1944-7558-115.4.307

Musumeci SA, Ferri R, Colognola RM, Neri G, Sanfilippo S, Bergonzi P. Prevalence of a novel epileptogenic EEG pattern in the Martin-Bell syndrome. American Journal of Medical Genetics.1988; 30(1-2):212-207. PMID:3177446 DOI: 10.1002/ajmg.1320300120

Musumeci SA, Ferri R, Elia M, Colognola RM, Bergonzi Pm Tassinari CA. Epilepsy and Fragile XSyndrome: a follow-up study. American Journal of Medical Genetics. 1991 Feb 1; 38(2-3):513-511. PMID:2018098 DOI:10.1002/ajmg.1320380276

Musumeci SA, Hagerman RJ, Ferri R, Bosco P, DallaBernadino B, Tassinari CA, DeSarro GB, Elia M. Epilepsy and EEG findings in males with fragile X syndrome. Epilepsia. 1999 Aug; 40(8):1099-1092. PMID: 10448821DOI: 10.1111/j.1528-1157.1999.tb00824.x

Palmer KK, Gordon JS, Coston GN, Stevenson RE. Fragile X syndrome IV. Speech and language characteristics. Proceedings of the Greenwood Genetics Center. 1988; 7:97-93.

Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G. An assessment of screening strategies for fragile X syndrome in the UK. Health technology assessment (Winchester, England). 2001; 5(7):95-1. PubMed PMID: 11262423.

Pouya A, Abedini S, Mansoorian N, Behjati F, Nikzat N, Mohseni M, Nieh S, AbbasiMoheb L, Dravish H, Mohajemi G, Banihashemi S, Kahrizi K, Ropers H, Najmabadi H. Fragile X syndrome screening of families with consanguineous and non-consanguineous parents in the Iranian population. Eur J Med Genet. 2009 Jul; 52(4):173-170. PMID:19361583 Doi:10.1016/j.ejmg.2009.03.014

Powis L, Oliver C. The prevalence of aggression in genetic syndromes: a review. Research in Developmental Disabilities. 2014 May;35(5):1071-1051. PMID:24594523 Doi:10.1016/j.ridd.2014.01.033

Prouty LA, Rogers C, Stevenson RE, Dean JH, Palmer KK, Simensen RJ, Coston GN, Schwartz CE. Fragile X syndrome: Growth, development, and intellectual function. American Journal of Medical Genetics. 1988 May; 30(1-2):142-123. PMID: 3177438 DOI: 10.1002/ajmg.1320300111

Qiu LF, Hao YH, Li QZ, Xiong ZQ. Fragile X syndrome and epilepsy. Neurosci Bull. 2008 Oct 1; 24(5):344-338. PMID: 18839028 doi: 10.1007/s12264-008-1221-0

Roberts J, Long SH, Malkin C, Barnes E, Skinner M, Hennon EA, Anderson K. A Comparison of Phonological Skills of Boys with Fragile X Syndrome and Down Syndrome. Journal of Speech, Language, and Hearing Research. 2005 Oct; 48(5):995-980. PMID:16411789 doi:10.1044/1092-4388(2005/067)

Rogers SJ, Wehner DE, Hagerman R. The behavioral phenotype in Fragile X: Symptoms of autism in very young children with Fragile X Syndrome, idiopathic autism, and other developmental disorders. J. Dev. Behav. Pediatr. 2001 Dec; 22(6):417-409. PMID:11773805

Ropers HH, Hamel BC. X-linked mental retardation. Nature Reviews Genetics. 2005 Jan; 6(1):57-46. Doi:10.1038lnrg1501

Sabaratnam M, Vroegop PG, Gangadharan SK. Epilepsy and EEG findings in 18 males with fragile X syndrome. Seizure. 2001 Jan; 10(1):63-60. PMID:11181100 Doi:10.1053/seiz.2000.0492

Saldarriaga W, Tassone F, González-Teshima LY, Forero-Forero JV, Ayala-Zapata S, Hagerman JR. Review article: Fragile X syndrome. Colomb Med. 2014;45(3):198-190.

Schopmeyer BB, Lowe F, Eds. The fragile X child. San Diego: Singular Publishing. c1992.

Sherman SL, Jacobs PA, Morton NE, Froster-Iskenius U, Howard-Peebles PN, Nielsen KB, Partington MW, Sutherland GR, Turner G, Watson M. Further segregation analysis of the fragile X syndrome with special reference to transmitting males. Hum Genet. 1985 Apr; 69(4):299-289. PMID: 3838733 DOI: 10.1007/BF00291644

Snow K, Doud LK, Hagerman R, Pergolizzi RG, Erster SH, Thibodeau SN. Analysis of a CGG sequence at the FMR-1 locus in fragile X families and in the general population. American journal of human genetics. 1993 Dec; 53(6):1228-1217. PMCID: PMC1682501

Sullivan K, Hatton D, Hammer J, Sideris J, Hooper S, Ornstein P, Bailey DB. ADHD symptoms in children with FXS. Am J Med Genet. 2006 Oct 4; 140A(21):2288-2275. DOI: 10.1002/ajmg.a.31388

Vieregge P, Froster-Iskenius U. Clinico-neurological investigations in the fra(x) form of mental retardation. Journal of Neurology. 1989 Feb; 236(2):92-85. DOI:10.1007/BF00314402

Wheeler AC, Raspa M, Bishop E, Bailey Jr DB. Aggression in fragile X syndrome. Journal of Intellectual Disability Research. 2016 Feb; 60(Pt. 2):125-113. PMID: 26628097 DOI:10.1111/jir.12238