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

Norah Fahad Al-Hur 1* Entissar Alsuhaibani 2
1. Master degree in Zoology, King Saud University, Riyadh
2. Professor of genetic, King Saud University, Riyadh

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 estimated 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 affected 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-linked 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 CCG 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>
<thead>
<tr>
<th>Age</th>
<th>No. of Males</th>
<th>%</th>
<th>No. of Females</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>7</td>
<td>43.75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-10</td>
<td>3</td>
<td>18.75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11-15</td>
<td>3</td>
<td>18.75</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>16-20</td>
<td>2</td>
<td>12.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1</td>
<td>6.25</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Feature</th>
<th>No. of Full FXS</th>
<th>Percentage</th>
<th>No. of premutation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consanguinity</td>
<td>11/15</td>
<td>73.33</td>
<td>2/2</td>
<td>100</td>
</tr>
<tr>
<td>Family history of ID</td>
<td>1/15</td>
<td>6.66</td>
<td>1/2</td>
<td>50</td>
</tr>
<tr>
<td>ID levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>6/15</td>
<td>40</td>
<td>1/2</td>
<td>50</td>
</tr>
<tr>
<td>Moderate</td>
<td>5/15</td>
<td>33.33</td>
<td>1/2</td>
<td>50</td>
</tr>
<tr>
<td>Severe</td>
<td>4/15</td>
<td>26.66</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3. Consanguinity in Families and FSX siblings

<table>
<thead>
<tr>
<th>Consanguineous</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Families with FSX siblings</th>
<th>No. of Family Males</th>
<th>FSX siblings Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consanguineous</td>
<td>7</td>
<td>77.78</td>
<td>3</td>
<td>1 3 -</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-Consanguine</td>
<td>2</td>
<td>22.22</td>
<td>1</td>
<td>2 2 1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4 summarizes the associated conditions found in 14 FSX 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 FSX males

<table>
<thead>
<tr>
<th>Associated Conditions</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonia</td>
<td>1</td>
<td>7.14%</td>
</tr>
<tr>
<td>ASD</td>
<td>2</td>
<td>14.3%</td>
</tr>
<tr>
<td>Abnormal laughter</td>
<td>1</td>
<td>7.14%</td>
</tr>
<tr>
<td>Speech Delay</td>
<td>2</td>
<td>14.3%</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>4</td>
<td>28.57%</td>
</tr>
<tr>
<td>Aggressive Behavior</td>
<td>2</td>
<td>14.3%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>7.14%</td>
</tr>
<tr>
<td>Reckless Behavior</td>
<td>1</td>
<td>7.14%</td>
</tr>
</tbody>
</table>

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 FSX 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 FSX 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 varys 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 shown 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


PMID:8192902


