Fragile X syndrome: a clinico-genetic study of mentally retarded patients in Kuwait

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متلازمة الصبغي X الهش: دراسة سريرية وراثية على مرضى متخلّفين عقلياً في الكويت

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الخلاصة: أجريت في الكويت دراسة استباقية للتحري، شملت 182 من الذكور المصابين بالتأخر العقلي الذين استوفوا خمساً أو أكثر من المعايير السريرية لتشخيص متلازمة الصبغي X الهش، وذلك باستخدام اختبار التفاعل السلسلي للبوليميراز. وقد وجد أن عشرين مريضاً (11٪) على درجة عالية من الشك بأنهم مصابون بمتلازمة الصبغي X الهش الناجمة عن طفرة في موقع FRAXE، ولم يكن لدى أي من المدروسين طفرة في الموقع FRAXE. ومن بين العشرين كان 11 منهم (55٪) ممن تأكد أن لديه متلازمة الصبغي X الهش بتطبيق كل من أسلوب التفاعل السلسلي للبوليميراز والأسلوب الخلوي الوراثي. وقد كانت أهم الملامح السريرية تكرراً: تبارز الجبهة (100٪) وضخامة الأذنين (90٪) وتبارز الفك السفلي (90٪) وفرط الحركة (85٪). أما الملامح الأقل شيوعاً فتجنب التواصل بالعينين (45٪)، الذاتوية (45٪) والاختلاجات (30٪)، وكانت الخصيتان ضخمتين في 55٪ من الحالات. وكانت المعايير السريرية في فترة ما قبل البلوغ وما بعده مختلفة.

ABSTRACT In a prospective study in Kuwait, 182 mentally retarded male patients who fulfilled 5 or more clinical criteria of fragile X syndrome were screened using polymerase chain reaction (PCR) testing. Twenty patients (11%) were highly suspected of having fragile X syndrome due to mutation at the *FRAXA* locus; none had mutation at the *FRAXE* locus. Of these, 11 (55%) were confirmed fragile-X-positive by both cytogenetic and PCR techniques. The most frequent clinical features were: prominent forehead, high arched palate, hyperextensible joints, long ears, prominent jaw, height > 10th centile and attention-deficit hyperactivity. Less common were avoidance of eye contact (45%), autism (45%) and seizures (30%). Large testes were found in 55% of cases. Pre-pubertal and post-pubertal clinical criteria were different.

Syndrome du chromosome X fragile: étude clinico-génétique chez des patients présentant un retard mental au Koweït

RESUME Dans une étude prospective au Koweït, 182 patients de sexe masculin présentant un retard mental qui remplissaient 5 ou plus des critères cliniques du syndrome de l'X fragile ont fait l'objet d'un examen PCR (amplification en chaîne par polymérase). Vingt patients (11 %) étaient fortement suspectés d'être atteints de ce syndrome du fait d'une mutation au niveau du locus *FRAXA* ; aucun patient n'avait de mutation au niveau du locus *FRAXE*. Les techniques de cytogénétique et de PCR ont permis de confirmer que 11 (55 %) de ces patients étaient X-fragiles. Les caractéristiques cliniques les plus courantes étaient un front proéminent, un palais ogival, un relachement des articulations, de grandes oreilles, une mâchoire proéminente, une taille superiente a cilli correspondant au 10e contile et une hyperactivité avec troubles de l'attention. Le fait d'éviter le contact visuel (45 %), l'autisme (45 %) et les convulsions (30 %) étaient moins courants. On a observé dans 55 % des cas une macro-orchidie. Les critères cliniques prépubertaires et postpubertaires étaient différents.

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Introduction

Fragile X syndrome is the second most common cause of inherited mental retardation with an estimated prevalence of 0.4–0.8 per 1000 males and 0.2–0.6 per 1000 females [*1*]. More recent studies using molecular genetic testing of the gene for fragile X have estimated a prevalence of 16:100 000 to 25:100 000 males affected with the syndrome [*2–4*]. The syndrome is mainly characterized by a variable degree of mental retardation, typical long and narrow facial appearance, large ears and large testes [*5,6*]. It is inherited as an X-linked dominant trait with reduced penetrance, i.e. only 80% of carrier males and 30% of carrier females are affected [*7*]. The responsible gene was identified in 1991 and was designated as 'fragile X mental retardation gene 1' (*FMR-1*) [*8*]. The fragile site was located at Xq27.3 and designated as *FRAXA*, which can be observed in the metaphase chromosome following selective culture conditions. Three other fragile sites, 1 proximal and 2 distal to *FRAXA*, have been cloned and termed *FRAXD*, *FRAXE* and *FRAXF* respectively.

Chromosome analysis using modified culture technique to induce fragile sites is no longer used due to its low sensitivity and increased costs compared with DNA-based techniques. Direct analysis of the CGG expansion mutation by Southern blotting has begun to replace cytogenetic analysis for the laboratory diagnosis of fragile X syndrome as it detects all the repeat expansion mutations including both full and premutation. However, blotting is a relatively expensive and labour-intensive procedure, particularly in the context of screening routine referrals.

The non-radioactive polymerase chain reaction (PCR) method specific for *FMR1* gene mutation detection is a very rapid test and has high sensitivity for normal and lower premutation repeat size. However, potential misdiagnosis from false negatives is rare due to cellular mosaicism.

The aim of the present study was to apply PCR testing for the first time in Kuwait and use it as a screening tool for detection of fragile X syndrome among a group of mentally retarded male patients who had clinical signs of the syndrome.

Methods

This prospective study in the Kuwait Medical Genetics Centre, Kuwait, started in January 2000 and lasted for 30 months.

Clinical study

The participants were 182 male patients referred with mental retardation of unknown etiology for clinico-genetic evaluation and diagnosis. A preconstructed sheet was used to record the following: nationality, age, parental age at patient's birth, consanguinity, birth weight height, occipto-frontal circumferance, craniofacial features, dermatological findings, skeletal findings, neurological and psychological features, speech, hyperactivity and the external genitalia. Associated anomalies and pedigree study were included too. Neurological and psychometric evaluations were conducted on each patient. Cognitive ability was assessed using the Wechsler Intelligence Scales (for Children or Adults). The severity of mental retardation was categorized into one of 3 groups according to the intelligence quotient [IQ] score: mild (50–70), moderate (35–50) and severe (20–35).

Patients were selected for the study if they fulfilled 5 or more criteria out of the most common 10 criteria associated with fragile X syndrome: mental retardation of unknown cause, family history of mental

retardation, large ears (ear length > 7.0 cm), large testes (testicular volume > 25 mL), long narrow face (inner canthal distance < 3.5 cm), prominent ears/jaws, high arched palate, calluses on hand, hyperactivity, avoidance of eye contact.

After informing the parents about the purpose of the study, peripheral vein blood samples (5 mL) were taken from each patient and stored in tubes with EDTA anticoagulant. Cytogenetic analysis was performed on blood samples cultured for 96 hours in folate-deficient tissue culture medium 199 with 5% fetal bovine serum.

Laboratory testing

Blood samples were obtained from healthy individuals for calibration of the test. The deoxyribonucleic acid (DNA) of the patients and control subjects was extracted from blood samples. The concentration and purity of DNA were measured in a PCR reaction before use. Two sets of primers were used for mutation detection of the *FRAXA* (*FXD1* and *FXE*) and *FRAXE* (598 and 603) loci. The primers were synthesized locally in our laboratory using 391 DNA synthesizers.

For amplification of the triplet repeat sequences at the *FRAXA* and *FRAXE* loci, the total volume of PCR mix was 25 µL, containing 100 mg of DNA mixed with 20 pmol of *FXD1* and *FXE* and 35 pmol of 598 and 603 primers to amplify *FRAXA* CCG and *FRAXE* CCG repeats respectively. It also contained: 2.5 µL of 10X polymerase buffer (Taq, BioCarta, San Diego, California, USA); 2.5 µL dimethyl sulfoxide; 200 µmol/L from each of dATP (deoxyadenosine 5'-triphosphate), dCTP (deoxycytidine 5'-triphosphate), dTTP (deoxythymidine 5'-triphosphate), 100 µmol of dGTP (deoxyguanosine 5'-triphosphate), 100 µmol 7-deaza-2-dGTP; and 0.25 µL (1.25 unit) of DNA polymerase enzyme (AmpliTaq Gold, BioCarta, San Diego, California, USA). The amplification was carried out using the Gene Amp PCR System 9700 (Applied Biosystems, Foster City, California, USA). The PCR was started by DNA denaturation for 10 min at 95 °C followed by 40 cycles of 95 °C for 1 min, 65 °C for 1.30 min and 72 °C for 2 min with a final extension for 7 min at 72 °C.

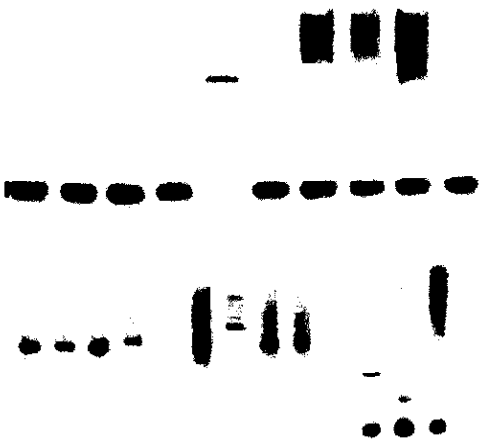
A total of 15 µL of PCR product were analysed by electrophoresis using 2% agarose gel, 1% agarose and 1% low melting agarose gel (Nusieve GTG, Cambrex, East Rutherford, New Jersey, USA) containing 0.5 µg/mL ethidium bromide.

Results

Out of 182 mentally retarded patients, 20 patients proved to be positive for fragile X syndrome by the PCR technique, giving an incidence of 11%. Figure 1 shows the amplification products of FRAXA and FRAXE.

Table 1 shows the clinical features of the fragile-X-positive patients. The frequency of siblings (85%) and relatives (70%) affected with fragile X syndrome was high. The most frequent clinical features among our patients were: mental retardation (100%), prominent forehead (100%), hyperextensible joints (100%), high arched palate (100%), large ears (90%), prominent jaw (90%), height > 10th centile (90%), attention-deficit hyperactivity (85%), stereotyped speech (85%) and biting hand movements (85%). Large testes (55%), avoidance of eye contact (45%), autistic-like behaviour (45%) and seizures (30%) were recorded less frequently (Table 1).

There were some differences between pre- or post-pubertal patients. All post-pu-



Lanes 1,4,6 and 7 are negative DNA samples of PCR products within normal range of repeat size (up to 224 bp)

Lanes 2,3,5 and 8 are suspected to be positive DNA samples with *FRAXA* mutation showing failure of amplification due to high repeat expansion.

Lanes 10 to 17 are amplification products of *FRAXE* locus of the same DNA samples showing that all cases are negative for *FRAXE* mutation

Lanes 19 to 22 are PCR amplification products of *FRAXA* locus using C7d GTP-For more confirmation of positive DNA samples

Lanes 9 and 18 are negative controls without DNA

Figure 1 Amplification products of *FRAXA* and *FRAXE*

Table 1 **Characteristic features of mentally retarded patients positive for fragile X syndrome by PCR**

Features	No. of patients	%
Stage of puberty		
Post-pubertal	11	55
Pre-pubertal	9	45
Family		
Siblings with fragile X	17	85
Relatives with fragile X	14	70
Behavioural characteristics		
Mental retardation	20	100
Attention-deficit hyperactivity	17	85
Stereotyped speech	17	70
Biting hand movements	17	70
Autistic behaviour	9	45
Avoidance of eye contact	9	45
Seizures	6	30
Physical characteristics		
Prominent forehead	20	100
High arched palate	20	100
Hyperextensible joints	20	100
Ear length > 75th centile	18	90
Prominent jaw	18	90
Height > 10th centile	18	90
Birth weight > 3 kg	17	85
Dry skin	15	75
Head circumference > 50th centile	13	65
Large testes	11	55
Flat feet	6	30
Gynaecomastia	5	25

No cases were found of abnormal heart, pectus excavatum or kyphosis.
n = *number of patients.*

bertal patients had macro-orchidism (100% of 11). The most prominent features among the 9 pre-pubertal fragile-X-positive patients were: prominent forehead, 100%), hyperactivity (100%), hyperextensible joints (89%), large ears (89%), high arched palate (89%), prominent jaw (78%), avoidance of eye contact (56%), stereotype speech (56%), autistic behaviour (33%) and seizures (22%). There was no difference in the severity of mental retardation among pre-pubertal and post-pubertal groups. Mild and severe mental retardation were equally found (around

45% in both groups), while moderate mental retardation was found in 1 patient in each group (around 10%).

There were major differences between the percentage frequency of the criteria among the positive fragile X patients and mentally retarded patients negative for fragile X (Table 2).

Cytogenetic analysis detected only 11 cases of fragile X syndrome (55% of the cases positive by PCR), an incidence of 6% among mentally retarded patients.

Discussion

Fragile X syndrome is the second most common cause of inherited mental retardation and is characterized by relative macrocephaly or normocephaly, variable degree of mental retardation, typical long and narrow facial appearance, large ears and large testes [*1,5,6*]. The dysmorphic features are seldom severe and many males in the past were referred purely with mental retardation.

The population prevalence of fragile X syndrome has been reported to vary from 0.4–0.8 per 1000 in males and 0.2–0.6 per 1000 in females [*3,9,10*]. More recent studies using molecular genetic testing of *FMR-1* have estimated a prevalence of 16:100 000 to 25:100 000 males affected with fragile X syndrome [*2–4*]. The prevalence of females affected with fragile X syndrome is presumed to be approximately one-half of the male prevalence. A population based prevalence study of affected African–American males revealed a higher estimate, 39:100 000 to 78:100 000 at 95% confidence interval [*11*].

Among mentally retarded patients, the incidence of fragile X syndrome varies from 3.5% to 8% [*12,13*], an incidence lower than that reported here (11%). Our higher incidence may be due to selection of the patients based on the most prominent criteria of fragile X syndrome, which increases the likelihood of finding fragile X positives. Alternatively, the PCR technique might increase the detection rate: we found 11% of mentally retarded patients were

Table 2 **Frequency of fragile X traits in fragile-X-positive and -negative mentally retarded patients**

Clinical sign	Fragile-X-positive ($n = 20$) %	Fragile-X-negative ($n = 162$) %	*P*-value
Long narrow face	100	38	< 0.0001
High arched palate	100	21	< 0.0001
Large ears	90	29	< 0.0001
Hyperactivity	85	18	< 0.0001
Large testes	55	10	< 0.0001
Avoidance of eye contact	45	7	< 0.0001

n = *number of patients.*

positive using PCR compared with 6% using cytogenetic analysis. The symptoms and signs of mental retardation are variable, and hyperactivity and seizures are common features. The degree of mental retardation varies from mild to severe, depending on the age group of the selected cases [*14–16*].

Brain scans in fragile X syndrome are usually normal. However, Mostofosky et al. studied 32 males with magnetic resonance imaging (MRI) and found the size of the cerebral posterior vermis was decreased, the hippocampus enlarged and the fourth ventricle increased [*17*]. A low frequency of fragile X cases (0.5%) was found among males with unexplained learning difficulties and language delay [*2,18,19*].

There are some specific features associated with fragile X syndrome. These are not necessarily found in all patients at different age groups and the frequency of each feature is age dependent. The most suggestive criteria for the diagnosis of fragile X syndrome found in this and other studies were: mental retardation, a family history of mental retardation, large or prominent ears, an enlarged face, attention deficit hyperactivity disorder and autistic-like behaviour. If a patient had 5 of these features then no case of fragile X would have been missed.

The frequency of macrocephaly (circumference > 50th centile) in our study was low (65%) compared with other reports [*20*] that the single most useful clinical criterion is head circumference above the 90th centile.

Macro-orchidism is difficult to identify early in life and it is frequently absent in the pre-pubertal period. The frequency of enlarged testes in our study was 55% overall, 100% in post-pubertal patients. This finding is consistent with other studies [*1,5,6,13*]. Accordingly, the presence of macro-orchidism is not necessary for the diagnosis of fragile X syndrome in the prepubertal child. The frequency of macro-orchidism in fragile X syndrome varies from 11% to 20% [*1,21*].

Other studies have suggested a relationship between autism and fragile X syndrome. However, a molecular study of 141 patients showed no association of autism with fragile X syndrome and the Xq27 region is not a candidate gene for autism [*22*]. Nevertheless, the present study showed a high incidence (45%) of patients who had autistic-like behaviour and most of them were in the post-pubertal stage. Other authors have reported a lower incidence of autism in fragile X syndrome (10.7%) [*1*].

Familial cases of fragile X have been reported before [23] but were not as high as reported in our study (85% and 70% of patients had affected siblings and relatives respectively). This incidence represents the frequency of fragile X syndrome among the siblings and relatives of fragile X patients themselves and not among the mentally retarded patients. Genetically, all mothers of isolated male cases of fragile X must be assumed to be carriers of a permutation or full mutation and about one-third of carrier females are retarded [24]. However, around 70% of females with a full mutation have below average IQ (less than 85%) [*25*]. Premutation was found to be behind the phenomenon of phenotypically normal transmitting males with no fragile sites [*21,26*]. This was confirmed by the discovery of an unstable CCG trinucleotide repeat sequence in the gene (*FMR-1*) [*27,28*]. Repeat length appears to be an important but not sufficient condition leading to instability of the *FMR-1* gene [*29,30*]. It has been suggested that expansion of the CCG trinucleotide repeat occurs during

early development and not during meiosis [*31,32*]. In males carrying full mutation, only sperm carried the premutation. However Malter et al. looked at the gonads of the fetuses carrying the full mutation and showed that full expansion alleles were detected in oocytes and in the testes of 13-week-old males [*33*].

Screening of fragile X syndrome can be carried out by different techniques: cytogenetics, molecular or antibody testing for *FMR-1* protein (using blood, chorionic villus or hair root samples) [*34–38*]. DNA testing is a cost-effective alternative to cytogenetic analysis, while antibody testing for *FMR-1* protein is rapid but of limited use (false positive results are high) and needs to be used in conjunction with DNA methods.

In conclusion, the criteria needed for diagnosis of fragile X syndrome will depend on the age of the patient. The laboratory diagnosis should depend on molecular studies rather than cytogenetic ones. PCR is the most suitable screening tool and should be confirmed by Southern blotting.

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Some facts on genetics

- 7 million children around the world are born annually with severe genetic disorders or birth defects.
- 90% of infants born with genetic disorders are found in developing countries, contributing significantly to global child mortality.
- Mutations have been characterized for most major single-gene disorders, and there is a growing understanding of the role of genes in complex diseases such as cancer, cardiovascular disease, diabetes and asthma.
- The final version of the entire Human Genome sequence was unveiled in April, 2003.
- Prevention and management of genetic disorders are published health priorities in some developing countries, for which the WHO Human Genetics Programme (HGN) is developing significant capacity building initiatives and normative and regulatory guidance.
- The top ten biotechnologies for improving health in developing countries have been identified by a WHO Human Genetics Collaborating Centre.

Source: WHO Fact sheets: Genomic Resource Centre; genetics and health (http://www.who.int/genomics/about/en/E_grc_final.pdf) and (http://www.who.int/genomics/en/E_hgn-_final.pdf)