GOOD CLINICAL PRACTICE RECOMMENDATIONS

FRAGILE X (*FMR1* GENE) TESTING

(BeSHG Workgroup on Clinical Genetics. September 2011)

1. DEFINITIONS

FMR1 normal allele: < 44 CGG repeats

Premutation allele: 55-200 CGG repeats*

Full mutation: > 200 CGG repeats

*smaller CGG repeats (45-55) can also be associated with repeat length instability upon transmission. Therefore the American College of Medical Genetics recommends maintaining a grey zone range of 45-55 CGG repeats.

2. FREQUENCE OF FRAGILE X PRE/FULL MUTATION

- males with the full mutation : 1/4000
- women carriers of the premutation : the frequency of FMR1 gene premutation carrier is estimated between 1/113 (for CGG repeats > 55)(Toledano-Alhadef H et al. 2001), to very low frequency in certain populations (Otsuka S et al. 2010). A frequency of 1/250 being mostly reported.
- screening of boys with learning difficulties reveals a 'new' case of fragile X syndrome in about 1%

3. TECHNOLOGY OF TESTING

The diagnostic procedures are mainly based on southern blotting and/or on direct amplification of the CGG repeat using flanking primers.

4. INDICATIONS FOR SCREENING

FMR1 testing is indicated in several clinical situations:

4.1. Fragile X syndrome

- FMR1 testing is indicated in the evaluation of patients (male and female) with intellectual disability, learning disorder, and/or autism.

- FMR1 testing is indicated as part of the first line of the etiological work-up in: Individuals of either sex with intellectual disability, developmental delay, or autism, in the presence of:

(a) physical or behavioral characteristics of fragile X syndrome*

and/or

(b) a family history of fragile X syndrome, if the pedigree structure indicates that the patient is at risk of inheriting the mutated gene

and/or

(c) male or female relatives with undiagnosed intellectual disability, and a pedigree structure indicating a possible X linked transmission.

Commenté [G1]: What is the difference with the first or previous indication ? repetitious ?

*The clinical features of Fragile X are subtle, and there is commonly a delay in making a specific diagnosis.

The degree of impairment can vary from profound handicap through to isolated learning problems but most affected males have a severe to moderate degree of impairment, with IQs in the range of 35–49.

Typical, but not specific behavioural problems include: avoidance of gaze, repetitive mannerism and obsessional traits, hyperactivity, repetitive speech patterns (unusual rhythm and perseverative phraseology).

Physical signs include: large heads for their age (greater than the 50th centile), large ears and a ‘long’ face. Macroorchidism is present only in 20% of prepubertal boys.

- FMR1 testing is recommended as part of the etiological work-up in individuals of either sex with intellectual disability, developmental delay, or autism. In these situations, FMR1 testing should be performed as part of a comprehensive genetic evaluation that includes cytogenetic analysis (CGH array). Cytogenetic studies are critical, since constitutional chromosome abnormalities have been identified as frequently or more frequently than fragile X mutations in mentally retarded individuals referred for fragile X testing.

4.2. Fragile X premature ovarian failure (FXPOI)

FMR1 testing is indicated for women who have reproductive or fertility problems associated with an elevated level of follicle stimulating hormone (FSH) before the age of 40 years.

Especially, but not only, if they have

(a) a family history of premature ovarian failure, and a pedigree history consistent with an X linked transmission.

and/or

(b) a family history of fragile X syndrome, if the pedigree structure indicates that the patient is at risk of inheriting the mutated gene.

and/or

(c) male or female relatives with undiagnosed intellectual disability and a pedigree structure indicating a possible X-linked transmission.

4.3. Tremor/ataxia syndrome (FXTAS)

FMR1 testing is indicated in men and women who are experiencing late onset intention tremor and cerebellar ataxia of unknown origin, especially if they have

(a) a family history of movement disorders, and a pedigree structure consistent with an X linked transmission.

and/or

(b) a family history of fragile X syndrome, if the pedigree structure indicates that the patient is at risk of inheriting the mutated gene.

and/or

(c) male or female relatives with undiagnosed intellectual disability, and a pedigree structure consistent with an X-linked transmission

and/or

(d) a brain MRI suggestive of FXTAS (white matter lesions in the middle cerebellar peduncles and/or brain stem)

4.4. Genetic counselling

4.4.1. Individuals seeking reproductive counselling

(a) Fragile X testing is indicated for a woman with a family history of fragile X syndrome, fragile X tremor/ataxia syndrome, or premature ovarian failure (in more than one family member) if the pedigree structure indicates that she is at risk of inheriting the mutated gene. Referral to a medical geneticist for counselling and assessment should be considered in these cases.

(b) Fragile X testing is indicated for a woman with a family history of undiagnosed intellectual disability, if the pedigree structure is consistent with the patient being at risk of inheriting the mutated gene.

4.4.2. Foetuses of known carrier mothers

Prenatal fetal testing via chorionic villus sampling or amniocentesis should be offered to women who are confirmed to be carriers of a premutation or full mutation of the FMR-1 gene.

Ideally DNA testing should be performed on cultured amniocytes obtained by amniocentesis after 14 weeks' gestation, but in this case the result is available around 18 weeks'gestation. DNA testing can be performed on chorionic villi obtained by CVS at 11 to 12 weeks' gestation, but the results must be interpreted with caution because the methylation status of the FMR1 gene is often not yet established in chorionic villi at the time of sampling. A follow-up amniocentesis may be necessary to resolve an ambiguous result.

4.4.3. "Cascade counselling"

FMR1 testing should be offered to relatives of carriers of an FMR1 full- or premutation. Simulations indicate that case-finding and cascade counselling can reach about half of the premutation carriers, if index cases in the family were used as starting points and testing extended to fifth-degree relatives. If performed in the case of a full FMR1 mutation, identified carrier would include most of those at the highest risk of having a child with fragile X syndrome, as premutation in these families has demonstrated its unstability.

Cascade counselling should be performed by a medical geneticist. Individuals should be tested at an appropriate life stage (in accordance to international ethics guidelines).

4.4.4. Population screening

Population carrier screening is not recommended at this time, except as part of a well-defined clinical research protocol.
While the DNA test is very accurate, two issues limit the application of FMR1 testing as a general prenatal population screening.

a. An uncertainty remains about the risks for women from the general population with FMR1 premutation with 45-55 CGG repeats. The low but uncertain risk of expansion to a full mutation in this population might lead to a high number of undue prenatal testing. Considerable work must be done before instituting general population screening protocols regarding identification and management of intermediate allele carriers.

b. The nature of different phenotypes associated with the FMR1 mutation in its premutation and full mutation forms and the inheritance pattern are complex, the approach to genetic counseling for different phenotypes including early onset disorder of intellectual disability, adult onset of premature ovarian failure, and a late onset disorder associated with neurodegeneration, all within the same family has not yet been addressed at a clinical level much less a population screening level.

5. REFERENCES

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