*Health Technology Assessment* 1997; Vol. 1: No. 4 (Executive summary)

**Review**

## *Executive summary*

# Screening for fragile X syndrome

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**Health Technology Assessment**
**NHS R&D HTA Programme**

# Executive summary

## Background and aim of review

In 1991, the gene responsible for fragile X syndrome, a common cause of learning disability, was discovered. As a result, diagnosis of the disorder has improved and its molecular genetics are now understood. This report aims to provide the information needed to decide whether to use DNA testing to screen for the disorder.

## How the research was conducted

A literature search of electronic reference databases of published and 'grey' literature was undertaken together with hand searching of the most recent publications.

## Research findings

### Natural history

Physical characteristics of fragile X syndrome include facial atypia, joint laxity and, in boys, macro-orchidism. Most affected males have moderate-to-severe learning disabilities with IQs under 50 whereas most females have borderline IQs of 70–85. Behavioural problems are similar to those seen with autism and attention-deficit disorders.

Although fragile X syndrome is not curable there are a number of medical, educational, psychological and social interventions that can improve the symptoms.

About 6% of those with learning disabilities tested in institutions have fragile X syndrome. Population prevalence figures are 1 in 4000 in males and 1 in 8000 in females.

### Genetics

The disorder is caused by a mutation in a gene on the X chromosome which includes a trinucleotide repeat sequence. The mutation is characterised by hyper-expansion of the repeat sequence leading to down-regulation of the gene. In males an allele with repeat size in excess of 200, termed a full mutation (FM), is always associated with the affected phenotype, whereas in females only half are affected. Individuals with alleles having repeat size in the range 55–199 are unaffected but in females the sequence is heritably unstable so that it is at high risk of expansion to an FM in her offspring. This allele is known as a pre-mutation (PM) to contrast it with the FM found in the affected individual. No spontaneous expansions directly from a normal allele to an FM have been observed.

### Screening strategies

The principal aim of screening for fragile X syndrome is to reduce the birth prevalence of the disorder, by prenatal diagnosis and selective termination of pregnancy, or by reducing the number of pregnancies in women who have the FM or PM alleles.

Possible screening strategies are: routine antenatal testing of apparently low risk pregnancies, pre-conceptual testing of young women, and systematic testing in affected families ('cascade' screening).

A secondary aim is to bring forward the diagnosis of affected individuals so that they might benefit from early treatment. Active paediatric screening and neonatal screening could achieve this but there is no direct evidence of any great benefit from early diagnosis.

### Screening tests

Cytogenetic methods are unsuitable for screening purposes. Southern blotting of genomic DNA can be used but is inaccurate in measuring the size of small PMs, there is a long laboratory turn-round time, and it is relatively expensive. The best protocol is to amplify the DNA using polymerase chain reaction on all samples and, when there is a possible failure to amplify, a Southern blot.

### Practical experience

There is little published information on the practical consequences of offering antenatal or pre-conceptual screening.

In one study, antenatal tests were offered to women about to have prenatal diagnosis for other conditions. They had to pay for themselves to be tested and uptake was only 21%. In another study, testing was offered to those with a family history of mental retardation but the uptake rate was not reported.

Pre-conceptual screening has only been reported among potential egg donors for *in vitro* fertilisation.

Four programmes of active cascade screening have been reported. In the largest study (conducted in Australia) in women with an FM or PM detected by screening and counselled, there was an estimated 26% reduction in births. In those who had further

children, similar acceptance rates for invasive prenatal diagnosis were reported in Australia (77%), New York, USA (50%) and Kuopio, Finland (100%).

Pregnancy is generally terminated when an affected male foetus is found and, from all the reported cases in the literature combined, 64% of female foetuses with an FM are also terminated.

In the UK and elsewhere, it is established practice for children with learning difficulties or developmental delay to be tested to exclude fragile X syndrome. However, only one active testing programme has been examined. In Colorado, USA, educators were trained to select school children believed to be at high risk for testing and 1% were found to have an FM.

Neonatal screening has not been tried in practice.

### Modelling allele dynamics

A model of allele inheritance was constructed. The critical parameters are the FM frequency (1 in 4000 for both sexes), PM frequency (1 in 273 for females, 1 in 800 for males), the risk of a PM allele expanding to FM (60–78% in families, 10% in the general population), and the reproductive fitness of individuals with an FM (50% for females, 0% for males).

### Assessment of screening

Antenatal screening can be expected to have a detection rate and a negative predictive value approaching 100%. The false-positive rate would be 0.4% and the positive predictive value 1 in 20.

It is known that invasive prenatal diagnosis has a high acceptability among carriers and that the termination rate for affected pregnancies is high, even for female foetuses. However, information on likely screening uptake is lacking so it is not possible to completely predict effectiveness.

Pre-conceptual screening is completely unevaluated but is unlikely to be a realistic option.

Within the affected families known to the cascade screening programme, there has been a dramatic reduction in affected births through avoidance of future pregnancies and prenatal diagnosis. However, there is no reliable information on the impact of this screening on the total population birth prevalence of fragile X syndrome.

Paediatric screening is widely practised but its effectiveness is unproven and neonatal screening is untried.

### Human and financial costs

Screening may result in psychological harm and, if invasive prenatal diagnosis is involved, there is also an approximately 1% foetal loss rate.

Care is needed to explain that the prognosis for a female with an FM cannot be predicted. Also, some apparently unaffected female carriers of mutations may have subtle cognitive problems and have difficulty understanding some of the complex information.

The average cost of preventing an affected birth was estimated as $14,200 (Australia, 1986) and $12,740 (USA, 1992). This is a small fraction of the estimated lifetime cost of care for an affected individual, which is a minimum of $1 million (USA).

Using the model, routine antenatal screening will cost between £90,000 and £143,000 depending on uptake. Although this is more than the cost of screening for Down's syndrome (£30,000) or cystic fibrosis (£40,000–104,000), technical developments may eventually lead to a reduction in cost.

## Main recommendations

Limited paediatric screening for fragile X syndrome and some cascade screening in affected families is currently being carried out at many UK centres. This is of clinical value and should continue. However, more research will be needed before any active screening programmes should be considered for implementation in the NHS.

- Studies should be carried out to assess the current practice of paediatric screening when there is developmental delay.
- There should be a national audit of the current practice of cascade screening in affected families.
- Research should be commissioned into the psychosocial implications of being identified as having a PM.
- The feasibility of routine antenatal screening should be assessed.
- A central register for all diagnoses should be established, based mainly on reports from DNA laboratories.

## Publication

Murray J, Cuckle H, Taylor G, Hewison J. Screening for fragile X syndrome. *Health Technol Assessment* 1997; **1**(4).

# NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health.



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http://www.soton.ac.uk/~hta ISSN 1366-5278