

## 9.13 Fragile X Syndrome

Fragile X is the commonest form of inherited learning disorder in males.

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### Epidemiology

- Prevalence 1 in 5700 in males with a full FRAXA mutation
- Males affected
- Females are unaffected carriers but may be mildly affected because of skewed X inactivation
- There is no maternal age effect but the allele (repeat) expansion is unstable and increases in length in successive generations (anticipation).
- Some individuals carry smaller expansions. (see Table)

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### Genetics

#### FRAXA

- Fragile X A (FRAXA) is caused by a CGG triplet repeat expansion within the FMR1 gene on the X chromosome at Xq27.3.
- With full mutations the FMR1 gene is methylated and no FMR1 protein is translated. Onset of symptoms is earlier in successive generations due to anticipation (see above).
- There is a strong correlation between the amount of fragile X protein (FMRP) made and intellectual function.

#### FRAXE

- FRAXE has a prevalence of less than 1 in 23000.
- It is due to GCC triplet expansions in the FMR2 gene located at Xq28.
- Compared to FRAXA the phenotype is milder.
- As with full mutations of FMR1 gene, large expansions in FMR2 are methylated and no FMRP is produced.

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### Clinical presentation

#### Full mutations in males

- Intelligence quotient is significantly reduced in methylated-full mutation males to approximately 41.
- Developmental delay with hypotonia is common
- Speech and language varies from no speech to mild. Individual rarely can speak fluently.
- Behaviour is characterised by overactivity, impulsiveness, reduced concentration and poor social interaction often

punctuated by aggression. Autistic spectrum features are common.

- Many children have some degree of minor joint laxity.
- Macrocephaly
- Macro-orchidism
- Large ears

#### Full mutations in females

- Females are less affected because the normal X produces FMRP
- Level of FMRP correlates with IQ.
- Up to 50% of full mutation females have some learning or behavioural difficulty. Verbal skills tend to be better than physical skills.

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### Premutation alleles

- Only rarely are premutation carriers clinically affected.
- Children with learning problems and premutation alleles should be fully investigated to exclude other causes.
- Males may develop a progressive tremor and ataxia syndrome (FXTAS) associated with cerebellar tremor, ataxia, and brain atrophy leading to cognitive decline. The prevalence is unknown.
- Females with premutations are at risk of premature menopause (approximately 25% stop menstruating by age 40).

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### Intermediate alleles

Transmission of intermediate alleles from females are remarkably stable in the absence of a family history of fragile X. Intermediate alleles may potentially become full mutations in successive generations but by definition, only premutation alleles have the potential to expand to full manifesting mutations across one generation. Nolin et al (2003) found that approximately 205 of alleles in the range 49–54 were unstable and could contract or expand.

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### Diagnosis

- Molecular DNA analysis of the FRAXA or FRAXE repeats size and methylation status.
- Carrier testing for at-risk relatives and prenatal diagnosis is possible.
- Testing for FRAXE is only done if there is a strong family history of X-linked mental retardation.

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### Management

- Referral to a developmental paediatrician

cian is essential to plan learning support and community liaison. Some but not all can manage mainstream schools.

- Recurrent otitis media leading to conductive deafness occurs in 60-80% of children
- Seizures are uncommon (20%) in children.
- Adult life often requires a degree of supported living.

#### Genetic Counselling:

- 25% risk for affected or carrier females to have severely affected sons
- Cascade screening of adult members is indicated.
- Males with a full or premutation mutation will pass this on to all daughters only. The repeat size is likely to stay stable.
- Females with a premutation are at equal risk of it expanding into a full mutation or remaining a premutation.

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## Prenatal Testing

- Possible by CVS at 12 weeks. Phenotype prediction in a female fetus carrying a full mutation is not possible.

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## References

Nolin, SL., Familial transmission of the fragile X CGG repeat in females with a premutation or intermediate alleles . Am J Human Genet. 2003. 72, 454-64

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### Full, Intermediate and normal allele size in FRAXA

Normal individuals	<45 repeats
Intermediate alleles	45-54 repeats
Premutation females and normal transmitting males	55-200 repeats
Affected males and full mutation carrier females	>200 repeats