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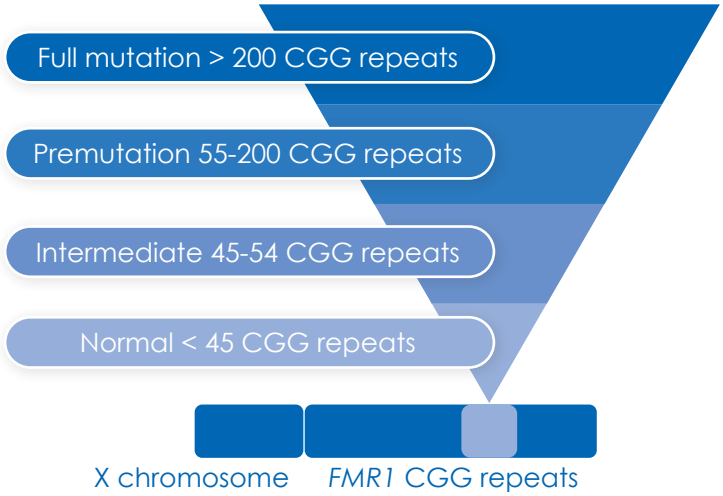
GENETIC TESTING FOR *FMR1* DISORDERS (INCLUDING FRAGILE X SYNDROME)

The *FMR1* disorders include fragile X syndrome (FXS), fragile X-associated tremor/ataxia syndrome (FXTAS), and fragile X-associated primary ovarian insufficiency (FXPOI).

FXS is the most common single gene cause of intellectual disability with an estimated prevalence of 1/4000 to 1/6000. Almost all cases are caused by the expansion of an unstable trinucleotide (triplet) (CGG) repeat in the 5' untranslated region of the *FMR1* gene.



The *FMR1* gene is located on the X chromosome and inheritance is thus X-linked. However, the genetics of *FMR1* disorders is complicated, due to the characteristics of the unstable triplet repeat. Most individuals in the general population have less than 45 CGG repeats, while individuals with FXS have >200 CGG repeats (termed a **full mutation**). Males with >200 CGG repeats present with developmental delay, intellectual disability (ID) and behavioural issues, commonly autism spectrum disorder (ASD), and a range of medical and physical features. Females who are heterozygous for the full mutation may exhibit variable features, with about half having borderline to mild intellectual disability and behavioural concerns.

Individuals who carry 55–200 CGG repeats are said to have a **premutation**. They do not have FXS, but are at increased risk for the other *FMR1* disorders. Approximately 40% of male and 8-17% of female premutation carriers present with features of FXTAS, usually after 50 years of age. These features include cerebellar ataxia, Parkinsonism, tremor, cognitive and psychiatric signs. FXPOI presents with early menopause (<40 years) or infertility in about 20% of female premutation carriers. Female premutation carriers have an increased risk of passing on their mutation, which can expand into the full mutation form, and are thus at risk of having a child with FXS. This risk depends, in part, on the size of the premutation. Females with a premutation have a greater chance of the repeat region increasing into the next generation than do males with the premutation.

Individuals who carry 45–55 CGG repeats fall into the **intermediate/grey zone**. They are not thought to present with clinical features, or be at increased risk for having a child with a full mutation, but there is a risk for *FMR1* disorders in future generations.

Genetic counselling plays an essential role in the testing process and delivery of results for these conditions, as the individual, family and future reproductive implications are complex.

Genetic testing for *FMR1* disorders is most commonly requested by paediatric or adult neurologists, developmental paediatricians, and obstetricians or gynaecologists. The CGG expansion **cannot** be detected on karyotype (chromosome studies), array CGH or most NGS techniques (multigene panels or exome sequencing). Testing for *FMR1* disorders may be requested as a separate test in the investigation of unexplained developmental delay or intellectual disability, premature ovarian failure or adult onset ataxia or tremor, particularly in the context of a suggestive family history. *FMR1* full mutations account for 0.2–3% of individuals with ID/ASD. Premutations are found in 2–14% of cases of premature ovarian failure and 1–2% of adults with ataxia.

The **test method** uses extracted genomic DNA to determine the number of CGG repeats in the *FMR1* gene. Testing is performed using the AmplideX® PCR/CE *FMR1* kit with an accuracy of ±1 repeat. The PCR reaction utilises two primers that span the CGG region and a third primer complementary to the *FMR1* triplet repeat region. The fragments are sized on an Applied Biosystems Genetic Analyzer. This provides accurate sizing of alleles up to 200 CGG and identification of full mutation alleles >200 CGG.

Genetic testing for FXS and related disorders is offered at the Ampath Genetics Laboratory in Centurion. The specimen requirement is 3-5ml EDTA blood, sent at room temperature. The test-specific mnemonic is FRAX and a result can be expected after 2 weeks from receipt of the specimen at the laboratory.

For more information and/or genetic counselling referrals, contact Ampath Genetics on 012 678 1350/0645 or via email at geneticsclinic@ampath.co.za.

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