Fragile X

Fragile X syndrome is the most common inherited disorder causing intellectual disability, and similarly the most common X-linked disorder causing intellectual disability. It is among the top causes of intellectual disability next to Down syndrome, which is the most common cause of intellectual disability secondary to a chromosomal defect seen on karyotype. Fragile X is caused by an X linked dominant expansion of a trinucleotide repeat in the fragile X mental retardation 1 (FMR1) gene and predominantly affects males due to the X-linkage. The repeating triplet is CGG and expansion of this triplet causes a discontinuity of staining when cells are cultured in a folate deficient medium causing the chromosome to appear broken. Diagnosis is largely clinical looking for characteristic findings such as intellectual disability or mental retardation, long face, macroorchidism, large mandible, and large ears. Definitive diagnosis is made by DNA analysis to identify the trinucleotide repeat or a fragile X chromosome study. Owing to its inheritance pattern, the trinucleotide pattern expresses anticipation, which means successive generations with the disease will exhibit earlier and worsened symptoms from the previous generation. This effect is due to the accumulation of more trinucleotide repeats.

PLAY PICMONIC

Pathophysiology

Trinucleotide Repeat

DNA-strand with Repeats

Fragile X is caused by a repeating trinucleotide triplet CGG. In the normal population, the number of CGG repeats is less than 55. The presence of clinical symptoms can be detected when the repeat is amplified beyond 55 repeats.

CGG Repeats

C-Cat G-Glue G-Glue Repeats

The three nucleotide sequence CGG is present in abnormally high amounts, resulting in signs and symptoms of fragile X. Clinical presentation varies depending on the amount of trinucleotide repeats present.

FMR1 Gene

Farmer with (1) Wand in Jeans

In patients with fragile X syndrome, the expanded CGG triplet repeats are hypermethylated and the expression of the FMR1 gene (fragile X mental retardation 1 gene) is repressed, which leads to the absence of the fragile X mental retardation protein (FMRP) and subsequent mental retardation.

X-linked Dominant

X-suit and Dominoes

Fragile X is inherited in an X-linked dominant fashion.

Signs and Symptoms

Developmental Delay

Developmental-bus

Patients display developmental delay with an IQ in the range of 20-60.

Autism

Otter

Fragile X patients may display features which meet criteria for concomitant autism spectrum disorder. Autism is a pervasive developmental delay disorder characterized by language impairment as well as deficits in social interaction. The disorder is recognized by repetitive behavior and significant focus on objects rather than people.

Large Ears

Large Ears

Patients characteristically display large everted ears.

Large Jaw

Large Jaws

Patients characteristically display large mandible.

Long Face

Long Face

Patients characteristically display a long face.

Macroorchidism

Large-testes

Large testes are a distinctive feature in fragile X syndrome, which is observed in a high proportion of patients.