# *Fragile X Syndrome*

BY: NEHA SINGH, MADDALENA DAL POZZO AND HANA TAKAHASHI.

## ***Pathology***

Autosomal recessive, X-linked disease.

Inherited defect in 5' untranslated region of familial mental retardation-1 (FMR1) gene→ trinucleotide expansion→ abnormal length→↑ methylation→ promoter region methylation→ ↓ familial mental retardation protein (FMRP) synthesis→ clinical phenotype.


- **Trinucleotide (CGG) repeat expansion-:**

1. 45-54: intermediate expansion repeat number.
2. 55-200: carrier/premutation individual repeat number.
3. 200-4000: affected individual repeat number.

- **Inheritance-:**

❑ Autosomal recessive

❑ Mutations occur/worsen during oogenesis.

❑ Anticipation-: genetic mutation continue through pedigree→ ↑ length of expansion→ ↑ severity of disease.

## Signs and Symptoms

- Females are likely to show mild symptoms as compared to males.
- **Common features are as follows-:**

❑ Physical phenotype-: long face, prominent forehead, large ears, flat feet, low muscle tone, macro-orchidism after puberty, hyperextensible thumbs and finger joints and soft skin.

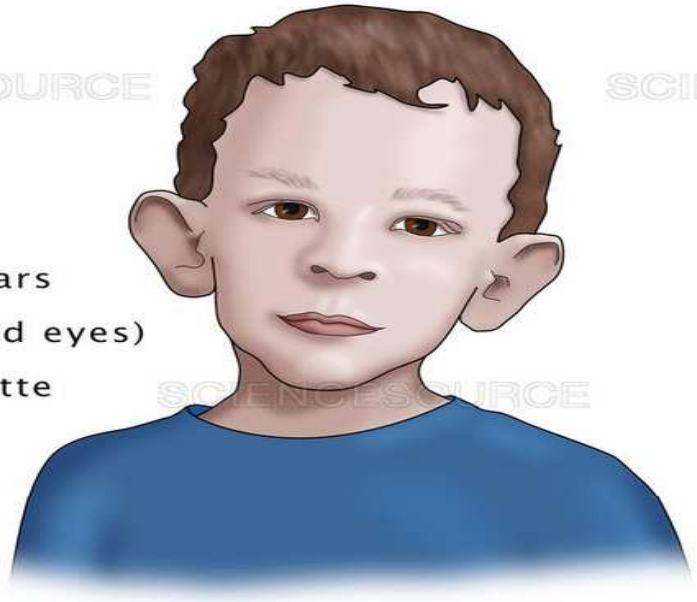
❑ Speech-: begin to talk later than other children.

❑ Vision-: strabismus, if left untreated can lead to amblyopia.

❑ Neurological-: intellectual disabilities, social anxiety, hypersensitivity and repetitive behavior, ADHD, fluctuating mood, self-harm, aggression and irritability.

# FRAGILE X SYNDROME

Broad forehead
Elongated face
Large prominent ears
Strabismus (crossed eyes)
Highly arched palette



Hyperextensible Joints
Hand calluses
Pectus Excavatum
(indentation of chest)
Mitral valve prolapse

Hypotonia (low muscle tone)
Soft, fleshy skin
Enlarged testicles
Flat feet
Seizures in 10%

## Complications

- **Behavioural features-:** Autism, ADHD, anxiety disorders.
- **Seizures**
- **Fragile X tremor/ataxia-:** observed in carrier/premutation individuals.

❑ Tremor/ataxia- parkinsonism.

❑ Short term memory loss, executive dysfunction (common).

❑ In females ovarian insufficiency; early menopause.

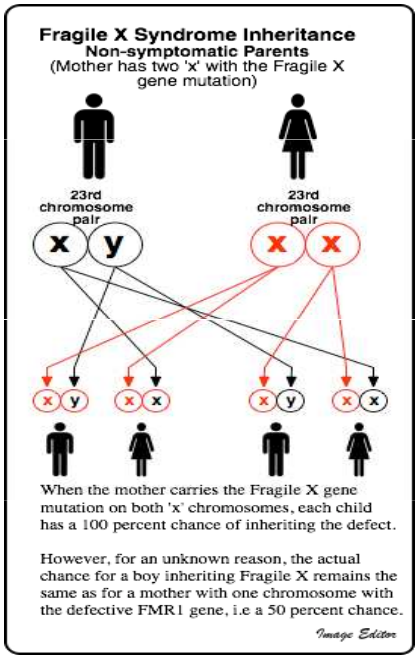
# Diagnosis

1. **Count CGG repeats on X-chromosome with the help of**

- Polymerase chain reaction (PCR).
- Methylation status with the help of southern blot analysis.

2. **Prenatal testing:**

- Chorionic villus sampling.
- Amniocentesis.




- **Medication-: symptoms directed management.**

❑ Behavioural features- ADHD Presentation-: > 5yr old- stimulant preparation e.g. methyphenidate.

❑ Anxiety/mood disorders- SSRI- SELECTIVE SEROTONIN REUPTAKE INHIBITORS.

❑ Seizures- anticonvulsants.

- **Psychotherapy**
- **Others-:**

❑ Special education.

❑ Vocational training.

❑ Antidepressants and antipsychotics.

❑ Early intervention.

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