



(REVIEW ARTICLE)



## Martin-Bell fragile X syndrome

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### Abstract

Fragile X syndrome (FXS) is one of the many disorders that are known and that are caused by some alteration or modification at the genetic level, one of the main characteristics of this type of syndrome also called Martin-Bell syndrome, is intellectual disability, as well as certain behaviors due to behavioral disorders, This is due to changes in the FMR1 gene, which is very important because it is responsible for producing the FMRP protein, which has the function of brain development, so when there is some kind of change in the gene and developing FXS the person may have little or no production of the FMRP protein.

**Keywords:** X chromosome; FMR1 gene; Intellectual disability; Disorders; Syndrome; Mutation

### 1. Introduction

Nowadays we are aware of the existence of several syndromes due to genetic variants, which have been discovered thanks to studies, explorations, analysis and research that have been carried out in detail over time, these genetic conditions impact in different ways and each of them contain their distinctive characteristics, which is why it has been of my interest to investigate and address information about Fragile X Syndrome (OMIM: 300624), since this is a very interesting topic that is very common for one of its main characteristics which is the intellectual disability, however they are not known by the genetic factor that causes it or that influences its development, we can say that it is a topic known colloquially, but not recognized phenotypically, therefore it is that I will address it in order to obtain information about how this syndrome is triggered by the genetic factors involved in the evolution of its distinctive characteristics.

The anomaly, also called Martin-Bell Syndrome, is due to a genetic mutation of the DNA that affects both the sex cells (eggs and sperm) as well as the FMR1 gene.

This disorder causes an unusual type of mutation, which is due to a repeated sequence of three letters of the DNA code, called triplet repeats, in this situation, the greater the number of these repeated sequences, the greater the probability that the person suffers severe alterations.

Studies have been conducted where it has been established that this syndrome occurs in both men and women, although there is a greater severe predominance in men.

### 2. Material and methods

For this review article, several sources of information on documents, articles and genetically oriented journals on Fragile X syndrome were used, thanks to the fact that several studies with different approaches have been previously carried out.

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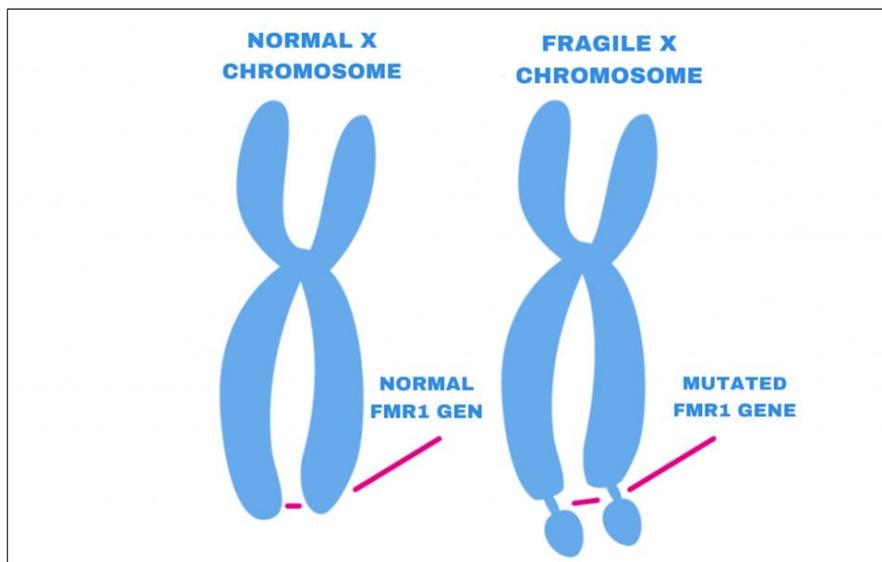
The focus for the selection of information was where data on the basis and characteristics of the genetic disorder FXS were found.

### 3. Etiopathogenesis

Fragile X syndrome is a modification that can occur in the genes of a person, it is considered as a neurodevelopmental disorder of genetic origin, which is hereditary and mainly affects the X chromosome, within this we find the FMR1 gene [Figure 1], which suffers from transcriptional silencing due to alterations in the DNA sequence, these modifications are called triplet repeats or trinucleotides (cytosine-guanine-guanine, CGG), as there are more than 200 triplet repeats in the Xq27 region. 3 of the X chromosomes, causes the FMR1 gene to be turned off and unable to produce the FMRP (Fragile X mental retardation protein) protein that is responsible for brain development. [Figure 2]. Thus, the number of CGG repeats a person has can determine whether they are at risk of having and inheriting FXS to their children.

- **Normal= 5-44 repeats:** does not have FXS, nor does it transfer an increased likelihood of FXS to their children. [1]
- **Intermediate= 45-54 repeats:** do not have FXS, are not at risk of having children with SFX, however, they may have a chance of having some symptoms related to this disorder. [1]
- **Premutation= 55-200 repeats:** do not have FXS, but could have or later present with associated disorders and their children would have premutation or full mutation. [1]
- **Full mutation= more than 200 repeats:** there is a full mutation of the FMR1 gene so they have FXS. [1]

It is important to mention that in the case of women, they have two X chromosomes, so they are less affected, because if one of them fails, they will always have the other X chromosome in charge of covering the anomaly of the other one, and this is where we can say that a woman with premutation has a 50% probability of transmitting to her children (girls or boys) the premutation or a complete mutation, In contrast, in the case of males, they only have a single X chromosome and it is more likely to have FXS, since it is impossible to replace the affected chromosome, since their other chromosome is the Y chromosome, so in this case the man with a premutation will transmit his premutation to his daughters, but not to his sons. [Figure 3]



**Figure 1** Adapted: X chromosome. Madrid Fragile X Syndrome Association

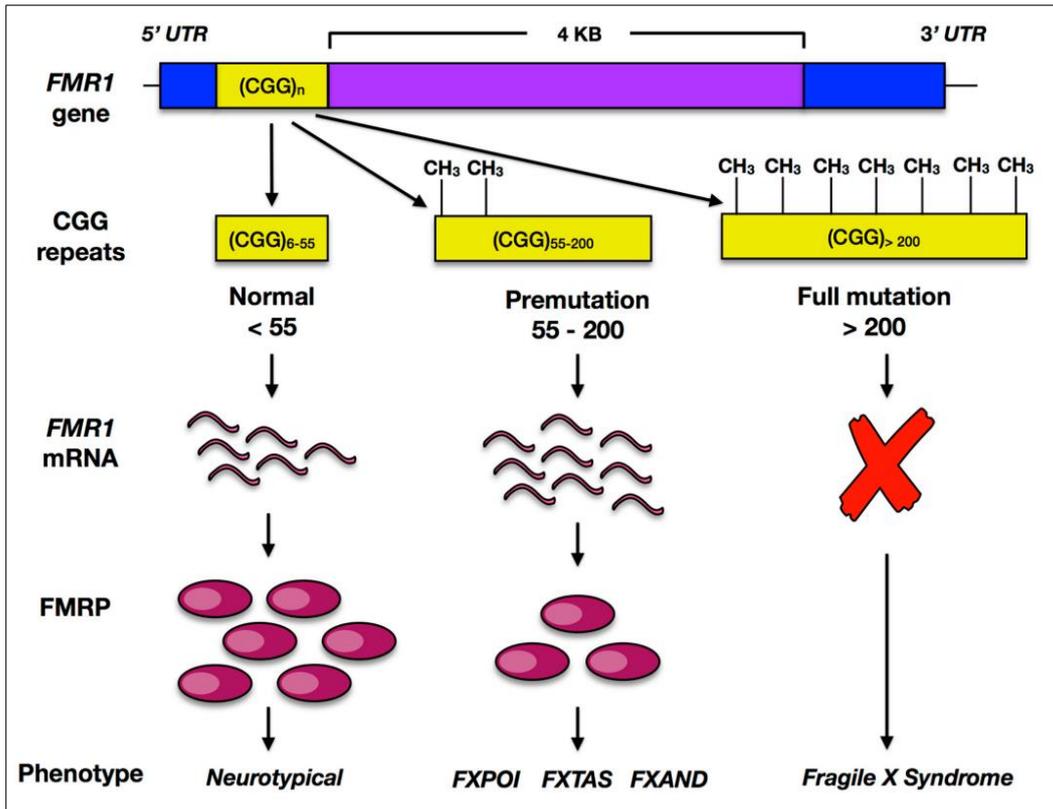


Figure 2 Adapted: The FMR1 gene and fragile X pathology. Guillermo, F., Milen, V. (2021)

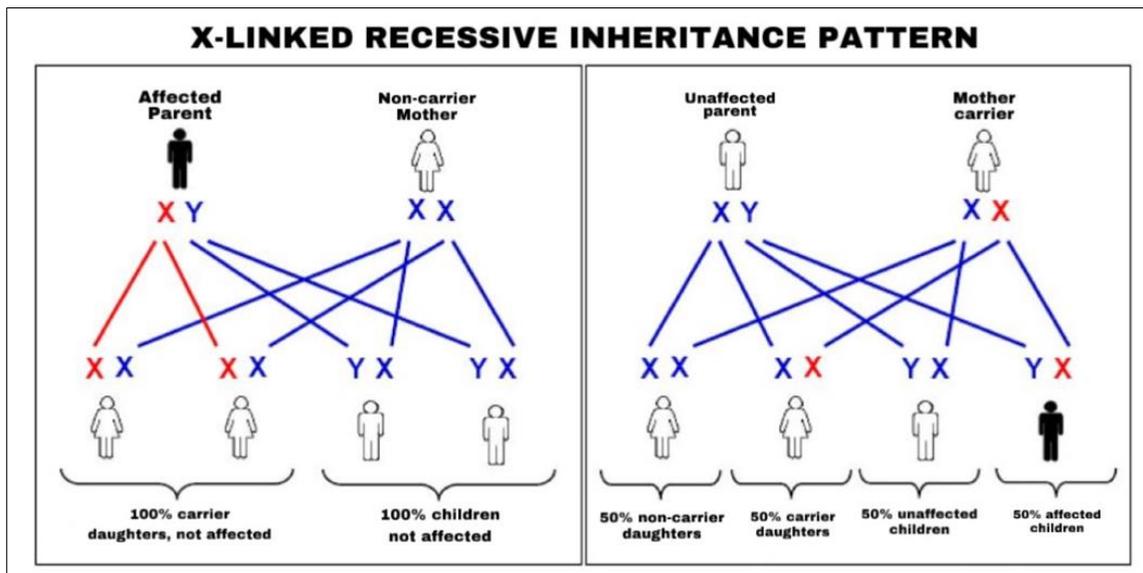
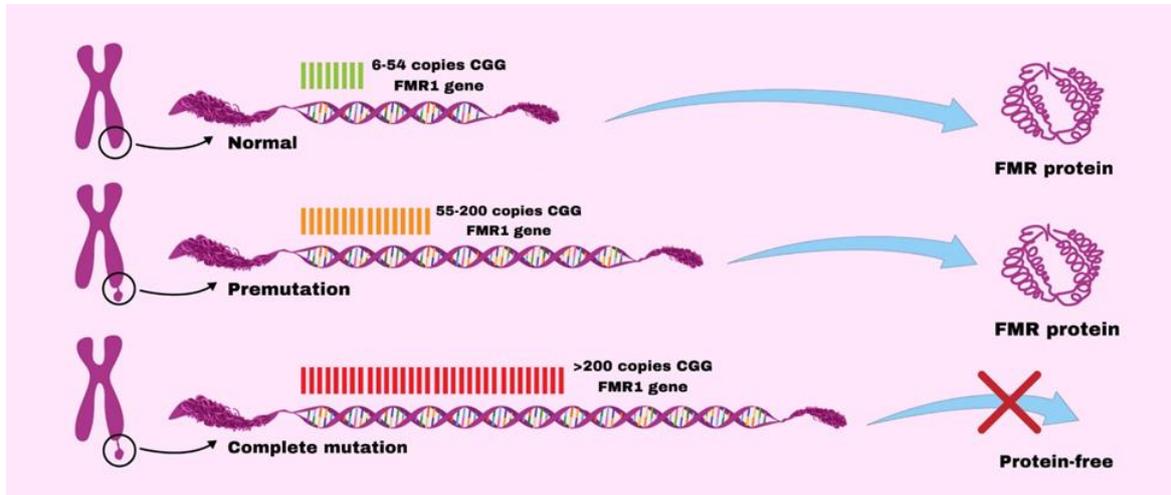


Figure 3 Adapted: Chromosome-linked pattern of inheritance X. www.bebemon.es

FMRP is a product of the FMR1 gene on the X chromosome, this protein is missing in patients who are affected by mutation and alteration of the DNA sequence. This protein assembles with RNA, other binding proteins and the homologous proteins FXR1P and FXR2P to form large ribonucleoprotein complexes. [2] [Figure 2]. These complexes regulate mRNA transport, translation and metabolism. [3] This activity is crucial for proper neuronal development, synaptic connectivity and plasticity, and dendritic architecture, which is why the production of FMRP is of utmost importance for proper brain development, since, when there is a mutation of the gene, the production of the protein is

completely inactivated and decreased [Figure 4] and this will lead to the affected person manifesting a series of alterations at a general level.

FMRP is found in the synapses, so its absence will alter synaptic plasticity, and this is important because it is involved in learning and memory, which is why one of the main characteristics of FXS is intellectual disability.



**Figure 4** Adapted: In the presence of a mutation on the X chromosome, the production of the protein is completely inactivated and decreases. Marta, B, G., Rebeca, R. (2017)

#### 4. Characteristics

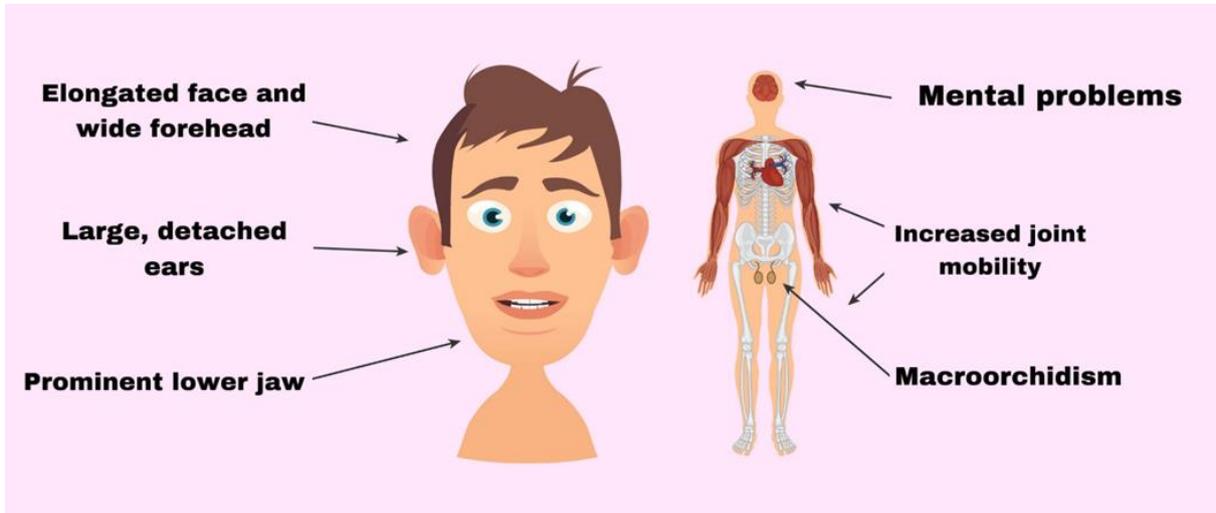
Fragile X syndrome presents some specific characteristics or features that allow us to identify the presence of this mutation, although not all patients with this disorder are the same or identical, we can find certain similarities.

- Behavioral and psychological characteristics. [4,5,6]
  - Intellectual disability (the most important and common).
  - Attention deficit
  - Hyperactivity
  - Behavioral problems (lack of control, tantrums, temper tantrums)
  - Social anxiety
  - Characteristic features of ASD (Autism)
  - Speech and language delay
  - Hand biting and hand clapping (stereotypies)
  - Crawling and walking later than normal
  - Avoid eye contact
- Physical characteristics. [4,5] [Figure 5]
  - Elongated and narrow face
  - Eyebrows are large and unattached
  - Broad and clear forehead
  - Prominent and large ears
  - Very large testicles (matriarchisms)
  - Hyperextensibility of finger joints
  - Flat feet with pronation
  - Arched palate
  - Prominent jaw
- Connective tissue-related features [4].
  - Muscle hypotonia
  - Strabismus
  - Frequent otitis
  - Irregular dentition

- Some cardiac problems (aortic artery dilatation or mitral valve prolapse)
- Parkinsonism
- Early menopause
- Dizziness
- Seizures

It is important to mention that people with FXS are very good at:

- Imitation ability
- Visual memory
- Sense of orientation
- Sense of humor



**Figure 5** Adapted: Characteristics of the Fragile X Syndrome. Marta, B, G., Rut, G, S., Sergio, R, C., Victoria, M. (2020)

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## 5. Diagnostic

To carry out the diagnosis of Fragile X syndrome the physician or geneticist must perform various tests, among them are the most basic which is by sight, i.e., observing the behavior of the patient, as well as the physical features that are characteristic of this disorder, and once this is done you can request or perform a blood test with specific techniques. Another type of analysis that is also useful for this mutation is to detect changes in the FMR1 gene that can lead to disorders associated with the fragile X chromosome or to find out if a person is a carrier of the gene that triggers the disease.

A good early diagnosis allows to start treatment earlier and can also alert other family members to the possibility of being affected by hereditary pathways, since as we have mentioned this mutation can be caused by inheritance from the parents.

Nowadays, thanks to modern testing techniques, prenatal and preimplantation diagnosis allows us to take measures to prevent the development of the mutation.

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## 6. Conclusion

Martin-Bell syndrome is one of the genetic disorders better known as Fragile X syndrome, within the analysis of information regarding this genetic modification, we can establish that it is one of the main factors by which you can get to develop what is intellectual disability, A disorder that is well known and of which many times there is no knowledge of its origin, in this review we can conclude that having a deficiency of the FMR1 gene on the X chromosome, it can trigger several alterations mainly mental and physical changes of the person who has developed FXS, this allows us to identify the characteristics of this genetic alteration. Thus, we can conclude that this type of mutation is frequent mainly because of its well-known characteristic which is the intellectual disability and where it occurs most often is in the case of men because they only contain a single X chromosome.

## Compliance with ethical standards

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### Disclosure of conflict of interest

No conflict of interest.

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