

Genetic Anticipation

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Abstract

Several genetic conditions show the phenomenon of genetic anticipation. Anticipation is a phenomenon where genetic disorders are passed on to the next generation genetic disorders become apparent at an earlier age with each generation. In most cases, an increase in the severity of symptoms is also noted. General anticipation occurs in trinucleotide repeat disorders, such as Huntington's disease and Myotonic dystrophy, where does it occur? dynamic mutations in DNA. All of these diseases have neurological symptoms.

Keywords: Genetic Anticipation; Genetics; Mutation;

Intorduction

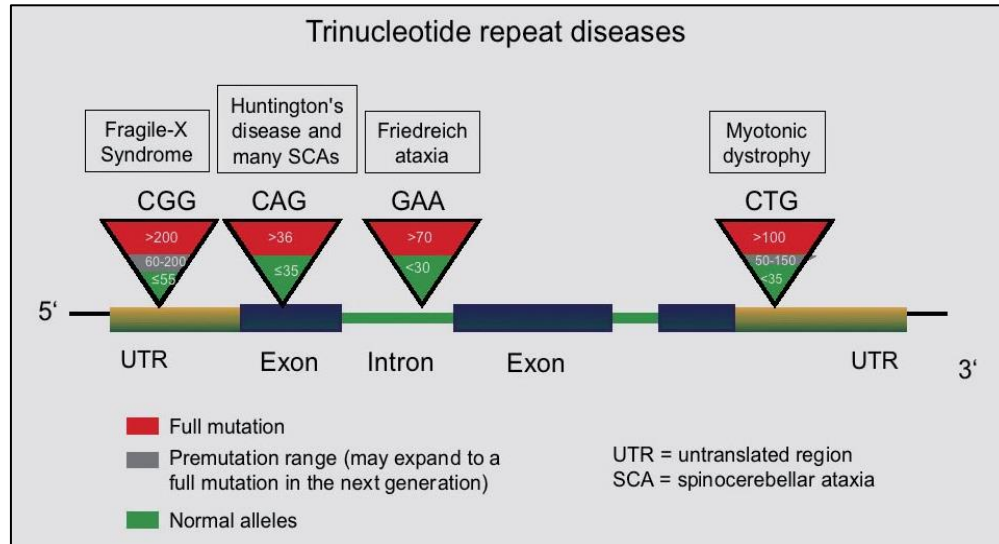
Anticipation is a phenomenon where genetic disorders are passed on to the next generation. Anticipation usually occurs with abnormalities caused by an unusual type of mutation called trinucleotide re-extension. A trinucleotide repeat is a sequence of three DNA building blocks (nucleotides) that are repeated several times in succession. DNA segments with an abnormal number of these repeats are unstable and prone to errors during cell division. The number of repetitions can change as the gene is passed from parent to child. If the number of repeats increases, this is known as trinucleotide repeat expansion. In some cases, trinucleotide repeats can occur until the gene stops functioning normally. This expansion causes the characteristics of some disorders to become more severe with each successive generation. Moreover, while in most individuals the trinucleotide repeat channel is harmless, expansion of the channel beyond a given outcome leads to pathogenic mutations (Lynn et al, 2010).

Method

The method used is a literature review, using literature searching. Library searches using website-based search tools, namely Google, Google Scholar, and PubMed using the keyword “(genetic anticipation OR anticipation OR anticipation in genetic)”. The selected literature is research articles, meta-analysis, systematic literature reviews, and narrative reviews published in the last 5 to 10 years that are relevant according to keywords. Literature outside of the aforementioned timeframe was not included in this paper. The selected literature is then collected and analyzed and then compiled into a scientific literature review.

Results and Discussion

Trinucleotide repeats were seen in a number of locus on human genome. They are found in introns, exon dan 5 ' or 3' UTR 's. They consist of a triple pattern nucleotide (e.g., CGG) that repeats itself several times. During meiosis, unstable repeats can undergo triplet expansion. In this case, the germ cells produced have a higher number of repeats than those found in somatic tissue (Yong et al. 2017).



Source: (Richard 2015)

For many loci, trinucleotide expansion is harmless. However, in some areas, the expansion has a detrimental effect that causes symptoms. When the trinucleotide repeat is within the protein-coding region, repeated expansion results in the production of a mutant protein with function gain. This is the case of Huntington's disease, in which the trinucleotide repeat encodes a long glutamine residue. If the repetition is in the untranslated area, it can affect the expression of the gene in which the repeat is found (ex. fragile X) or multiple genes through effects dominant-negative (e.g., Myotonic dystrophy) (Wikipedia, 2017)

To have an adverse effect, the number of repetitions must cross a certain threshold. For example, normal individuals have between 5 and 30 CTG repeats in the 3' UTR of DMPK, a gene that is altered in myotonic dystrophy. If the number of repetitions becomes more than 50, the person who is only slightly affected may only have cataracts. However, meiotic instability can cause a dynamic mutation that increases the number of repetitions in offspring inheriting the mutant allele. Once the copy number exceeds 100, the disease will manifest early in life (although the individual will still reach adulthood before the symptoms become apparent) and the symptoms will be more severe - including myotonia electrical. As numbers rise above 400, symptoms manifest themselves in childhood (US Department of Health & Human Services, 2018; Lynn et al, 2010 and Wikipedia, 2017).

In the genes associated with Huntington's disease and SCA (types 1, 2, 3, 6, 7, and 17), the CAG repeat channel is located within the coding sequence itself, with expansion resulting in the addition of the amino acid glutamine in the protein it encodes. In contrast, in the fragile X syndrome gene, the CGG repeat channel is located in the 5' untranslated region (UTR) with extension resulting in transcriptional repression and loss of protein function. To myotonic dystrophy (type 1), however, the underlying CTG abrogated expansion on chromosome 19q13 is located within the 3' UTR gene of the thyroid myotonic kinase (DMPK) gene. Mutant DMIPK mRNA causes abnormal splicing of several genes (by absorbing important RNA-binding

proteins) and thus results in the acquisition of toxic effects. Similarly, the toxic advantage of functional RNA effects is believed to be involved in SCA8 where CUG expansion is present at the 3' ends of the non-coding RNA, in SCA 12 where the CAG channel is at the 5' UTR of the associated gene and in the relatively rare myotonic dystrophy type 2, which is now known to result from a tetranucleotide repeat, CCTG, located in the first intron of the mouse protein gene zinc 9 (ZNF9) on chromosome 3q21 (US Department of Health & Human Services, 2018; Lynn et al, 2010 and Wikipedia, 2017).

Examples of diseases that show anticipation

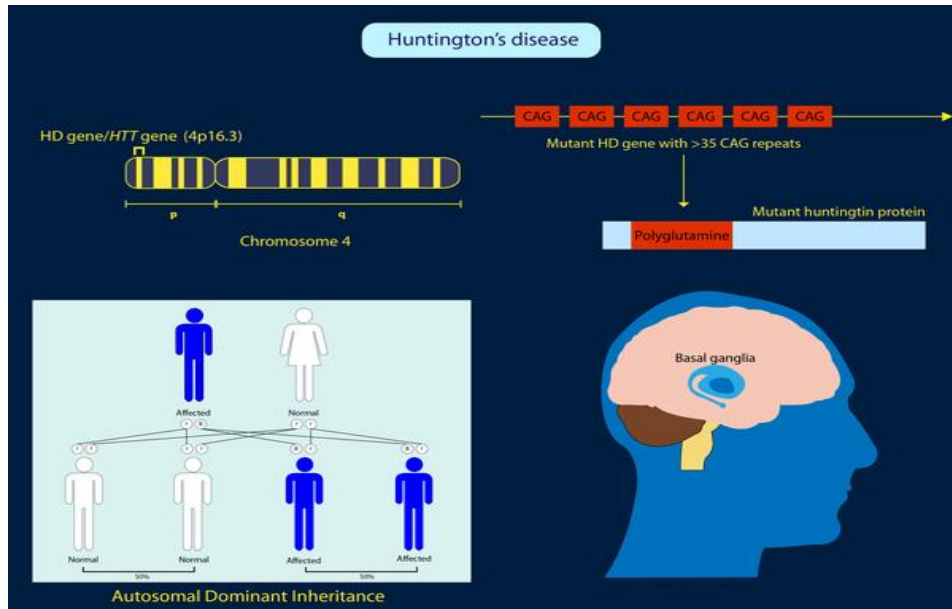
1. Huntington's disease

a. Description

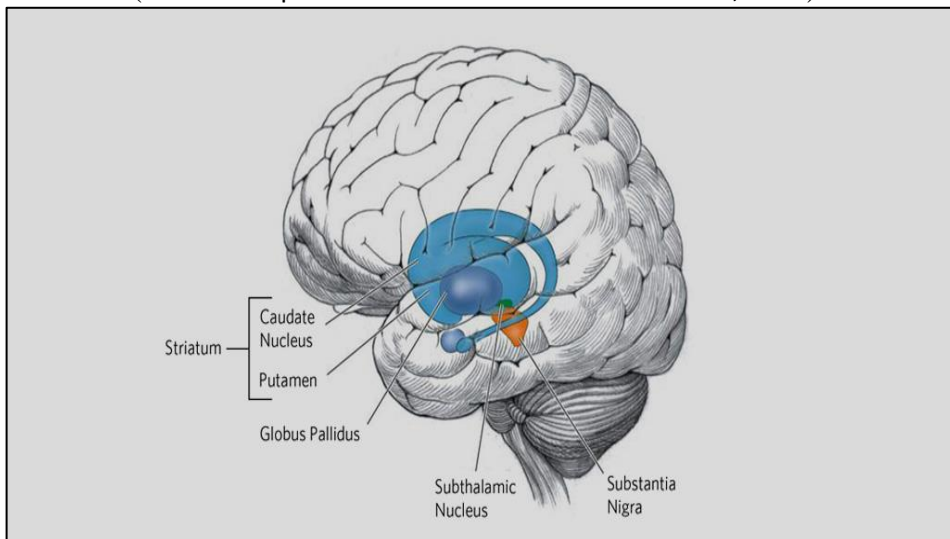
Huntington's Disease is a brain progressive disorder that causes uncontrollable movement, emotional problems, and loss of the ability to think (cognition).

Adult Huntington's disease, the most common form of the disorder, usually appears in your thirties or forties. Early signs and symptoms can include irritability, depression, involuntary movements, poor coordination, and difficulty learning new information or making decisions. Many people with Huntington's disease develop jerking movements or jerking movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have difficulty walking, speaking, and swallowing. People with this disorder also experience personality changes and decreased thinking and reasoning abilities. Individuals with the adult form of Huntington's disease usually live about 15 to 20 years after signs and symptoms begin.

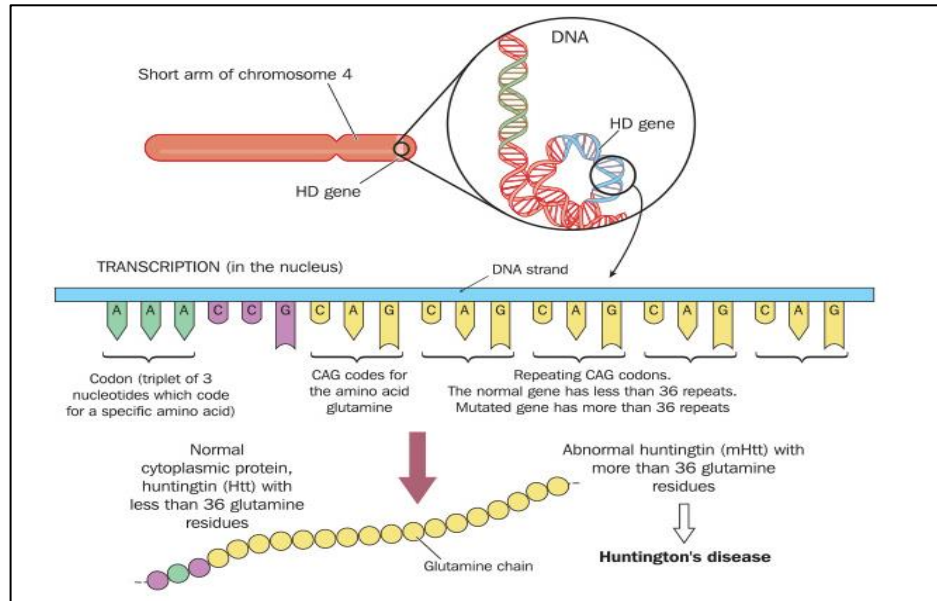
The less common form of Huntington's disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movement, clumsiness, frequent falls, stiffness, slurred speech, and drooling. School performance declines because thinking and reasoning abilities are impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington's disease tends to progress more rapidly than the adult-onset form. Affected individuals typically live 10 to 15 years after signs and symptoms appear (Department of Health & Services, Human 2018).



(Source: Department of Health & Services Human, 2018)



(Source: Huntington's Disease Society of America, 2017).



(Source: Huntington's Disease Society of America, 2017).

b. Frequency

Huntington's disease affects about 3 to 7 per 100,000 people of European descent. The disorder appears to be less common in some other populations, including people of Japanese, Chinese, and African descent (US Department of Health & Human Services, 2018).

c. Genetic changes

Gene mutations HTT causes Huntington's disease. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain (US Department of Health & Human Services, 2018).

The HTT mutation that causes Huntington's disease involves a segment of DNA known as CAG trinucleotide repeats. This segment consists of a series of three DNA building blocks (cytosine, adenine, and guanine) that occur several times in succession. Typically, the CAG segment is repeated 10 to 35 times in the gene. In people with Huntington's disease, the CAG segment is repeated 36 to more than 120 times. People with repeats of 36 to 39 CAG may or may not develop signs and symptoms of Huntington's disease, while people with repeats of 40 or more almost always develop the disorder (Imarisio et al. 2008)

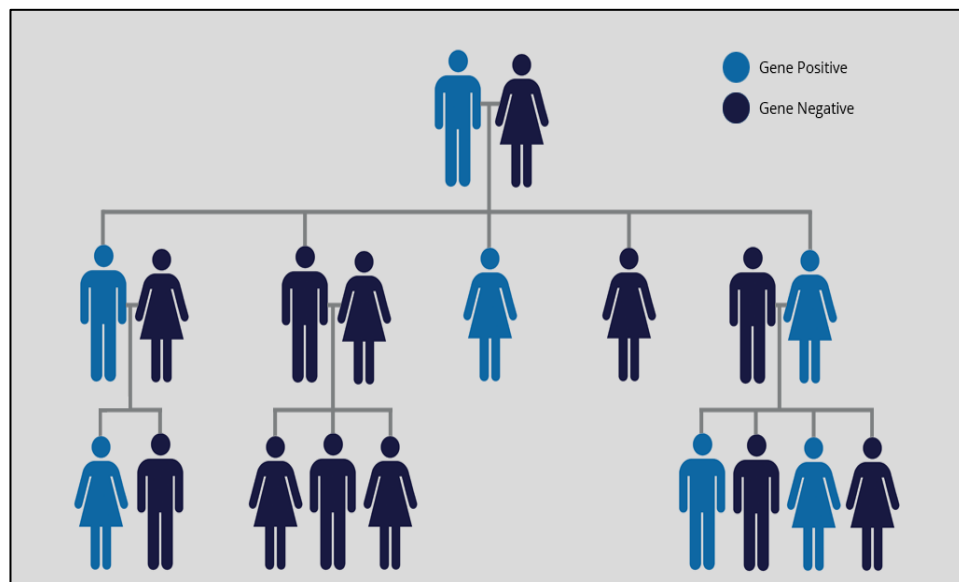
An increase in the size of the CAG segment leads to the production of an abnormal version of the huntingtin protein. These elongated proteins are cut into smaller toxic fragments that bind together and accumulate in neurons, interfering with the normal function of these cells. Dysfunction and eventual death of neurons in specific regions of the brain underlie signs and symptoms of Huntington's disease (Imarisio et al. 2008).

d. Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, meaning that one altered copy of the gene in each cell is sufficient to cause the disorder. Affected people usually inherit the altered gene from one affected parent. In rare cases, an individual with Huntington's disease does not have a parent with the disorder (US Department of Health & Human Services, 2018).

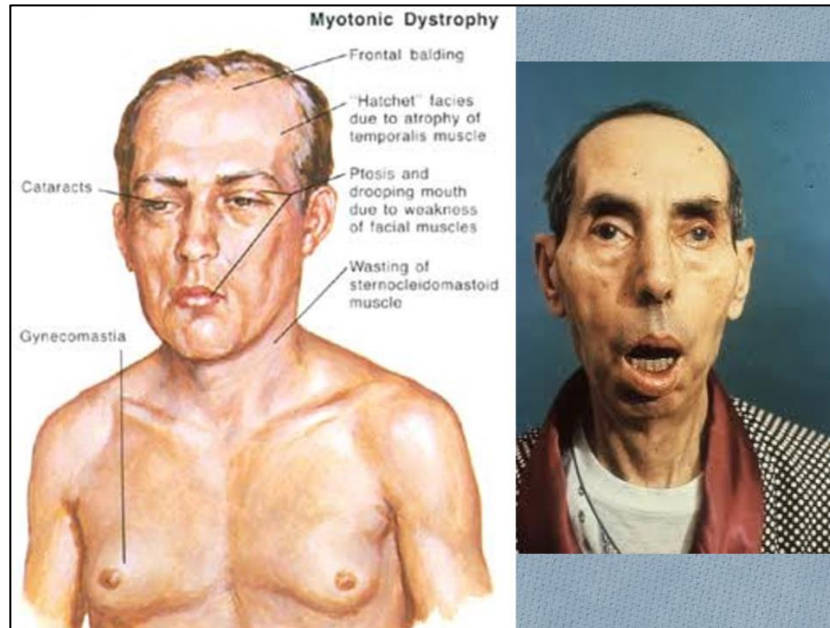
As a gene TheHTT is altered passed from one generation to the next, the size of the CAG trinucleotide repeats often increases in size. A large number of repetitions is usually associated with earlier onset of symptoms and symptoms. This phenomenon is called anticipation. People with the adult form of Huntington's disease typically have 40 to 50 CAG repeats in the HTT gene, while people with the juvenile form of the disorder tend to have more than 60 CAG beats.

Individuals who have 27 to 35 CAG repeats in the HTT gene do not develop Huntington's disease, but they are at risk of having children who will develop the disorder. As the gene is passed from parent to child, the size of the CAG trinucleotide repeat may extend into the range associated with Huntington's disease (36 or more repeats) (US Department of Health & Human Services, 2018 dan Warby et al., 1998) (Imarisio et al. 2008)



(Sumber: Huntington's Disease Society of America, 2017).

2. Myotonic dystrophy



(Source: <http://genetics4medics.com>)

a. Description

Myotonic dystrophy is part of a group of inherited disorders called muscular dystrophy. This is the most common form of muscular dystrophy that begins in adulthood.

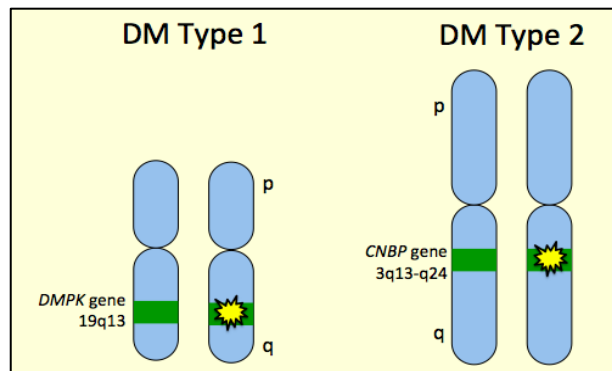
Myotonic dystrophy is characterized by muscle wasting progressive and weaknesses. People with this disorder often have prolonged muscle contractions (myotonia) and are unable to relax certain muscles after use. For example, a person may have difficulty releasing their grip on a knob or handrail. Also, affected people may dislike talking or temporarily locking their jaws.

Other signs and symptoms of myotonic dystrophy include clouding of the eye's lens (cataracts) and abnormalities of the electrical signals that control the heartbeat (heart conduction defects). In affected men, hormonal changes can lead to early balding and the inability to father a child (infertility). The picture of this disorder often develops in your twenties or thirties, although it can occur at any age. The severity of the condition varies greatly among affected persons, even among members of the same family (Ebralidze et al. 2004; Wheeler and Thornton 2007).

There are two main types of myotonic dystrophy: type 1 and type 2. Their signs and symptoms overlap, although type 2 tends to be milder than type 1. The muscle weakness associated with type 1 primarily affects the lower legs, hands, neck, and face. The muscle weakness in type 2 mainly involves the muscles of the neck, shoulders, elbows, and hips. The two types of myotonic dystrophy are caused by mutations in different genes.

A variety of myotonic dystrophy type 1, called congenital myotonic dystrophy, is present at birth. Characteristic features include weak muscles (hypotonia), legs inward and upwards (clubfoot), breathing problems, developmental delay, and intellectual disability.

Some of these health problems can be life-threatening (Ebraldidze et al. 2004; Wheeler and Thornton 2007).



(Source: <http://genetics4medics.com>)

b. Frequency

Myotonic dystrophy affects at least 1 in 8,000 people worldwide. The prevalence of the two types of myotonic dystrophy varies among different geographic and ethnic populations. In most populations, type 1 appears to be more common than type 2. However, recent research suggests that type 2 may be as common as type 1 among people in Germany and Finland (US Department of Health & Human Services, 2018).

c. Genetic Changes

Myotonic dystrophy type 1 is caused by mutations in the gene DMPK, whereas type 2 results from mutations in the gene CNBP. The specific function of this gene is not clear. The protein produced from the DMPK gene can play a role in communication within cells. It appears to be essential for the correct function of cells in the muscle heart, brain, and framework (which is used for movement). The protein produced by the CNBP gene is found primarily in the heart and skeletal muscle, which may help regulate the function of other genes.

Similar changes in the structure of the DMPK and CNBP genes lead to two forms of myotonic dystrophy. In each case, the DNA segment is repeated over and over again, forming unstable regions in the gene. The mutated gene produces a version messenger RNA Extended, which is the molecular blueprint of genes normally used to guide protein production. The abnormal messenger RNA forms clumps in cells that interfere with the production of many other proteins. These changes prevent muscle cells and cells in other tissues from functioning normally, leading to signs and symptoms of myotonic dystrophy (Ebraldidze et al. 2004; Wheeler and Thornton 2007).

d. Inheritance Pattern

Both types of myotonic dystrophy are inherited in the autosomal dominant pattern, meaning that one altered copy of the gene in each cell is sufficient to cause the disorder. In most cases, affected people have one parent with the condition.

Because myotonic dystrophy is passed from one generation to the next, the disorder generally starts earlier in life, and signs and symptoms become more severe. This

Genetic Anticipation

phenomenon, called anticipation, has been reported with both types of myotonic dystrophy. However, the evidence for anticipation appears to be strongest in myotonic dystrophy type 1. In this form of the disorder, anticipation is caused by an increase in the length of the unstable region of the gene DMPK. It is less clear whether anticipation occurs in type 2 myotonic dystrophy, and the mechanism is unknown. An unstable region in the gene CNBP does not appear to affect the age of onset of this disorder (Ebralidze et al. 2004; Wheeler and Thornton 2007).

e. Other Names for This Condition

- Dystrophia myotonica
- Myotonia atrophica
- Myotonia dystrophica

3. Sindrom Fragile X



(Source: Barry, 2017)

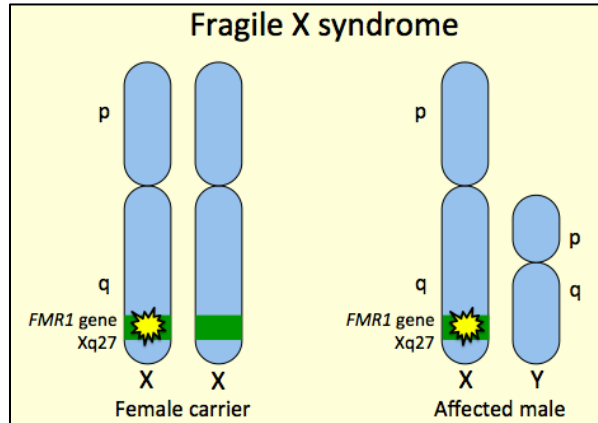
a. Description

Fragile X Syndrome is a genetic condition that causes a variety of developmental problems including learning disabilities and cognitive impairment. Usually, men are more severely affected by this disorder than women.

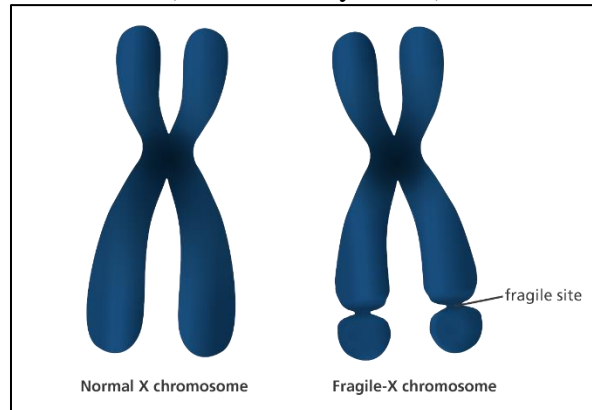
Affected individuals usually experience speech and language development delays by age 2. Most men with fragile X syndrome have mild to moderate intellectual disability, while about one-third of affected women have an intellectual disability. Children with fragile X syndrome also have restlessness and hyperactive behaviors such as restless or impulsive actions. They may have attention deficit disorder (ADD), which includes an impaired ability to sustain attention and difficulty focusing on certain tasks. About a third of individuals with

fragile X syndrome have features of an autism spectrum disorder that affects communication and social interactions. Seizures occur in about 15 percent of men and about 5 percent of women with fragile X syndrome.

Most men and about half of women with fragile X syndrome have distinctive physical features that become more pronounced with age. This feature includes faces that are long and narrow, large ears, prominent jaw and forehead, very flexible fingers, flat feet, and in males, enlarged testicles (macroorchidism) after puberty (USDepartment of Health & Human Services, 2018)



(Source: Barry, 2017)



(Source: Barry, 2017)

b. Frequency

Fragile X syndrome occurs in approximately 1 out of 4,000 men and 1 out of 8,000 women (USDepartment of Health & Human Services, 2018).

c. Genetic Changes

Mutations in genes FMR1 cause fragile X syndrome. The FMR1 gene provides instructions for making a protein called FMRP. This protein helps regulate the production of other proteins and plays a role in the development of synapses, which are special connections between nerve cells. Syncretic is very important for conveying nerve impulses.

Nearly all cases of fragile X syndrome are caused by mutations in which a DNA segment, known as the CGG triplet repeat, is extended in the FMR1 gene. Typically, this

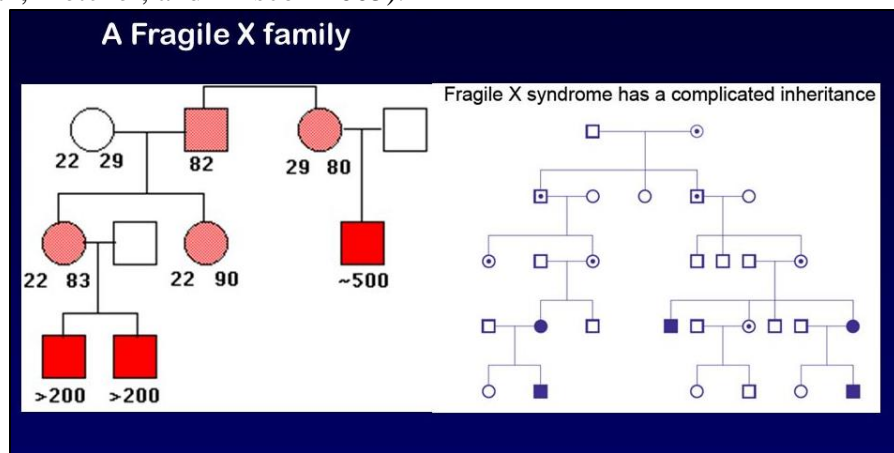
DNA segment is repeated from 5 to about 40 times. In people with fragile X syndrome, however, the CGG segment is repeated more than 200 times. The abnormal CGG segment extends silences the FMR1 gene, which prevents the gene from producing FMRP. Loss or deficiency (deficiency) of this protein impairs nervous system function and causes signs and symptoms of fragile X syndrome.

Men and women with 55 to 200 CGG segment repeats are said to have the FMR1 gene premutation. Most people with premutation are intellectually normal. However, in some cases, individuals with lower than normal FMRP premutation. As a result, they may have mild versions of the physical features seen in fragile X syndrome (such as protruding ears) and may experience emotional problems such as anxiety or depression. Some children on premutation may have learning disabilities or autistic-like behavior. Premutation is also associated with an increased risk of a disorder called lack of incidence primary ovary susceptible(FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS) (Koukoui and Chaudhuri 2007; Sherman, Pletcher, and Driscoll 2005).



d. Inherited Pattern

Fragile X Syndrome is inherited in X-linked dominant pattern . A condition is considered X-linked if the mutated gene that causes the disorder is located in X chromosome, one of the two sex chromosomes. (Y chromosome is chromosomes other sex.) Inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. X-linked dominant means that in women (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), mutations in the only copy of the gene in each cell cause this disorder. In most cases, men experience more severe symptoms of the disorder than women.

In women, premise of gene FMR1 on the X chromosome can develop into more than 200 CGG repeats in cells that develop into eggs. This means that women on premutation have an increased risk of having a child with fragile X syndrome. In contrast, premutation in men does not extend to more than 200 repetitions because it is passed on to the next generation. Men pass premutation only to their daughters. Their son received a Y chromosome, which does not include the FMR1 gene (Koukoui and Chaudhuri 2007; Sherman, Pletcher, and Driscoll 2005).



(Source: Barry, 2017)

Characteristics of Premutation and Fragile X Syndrome ¹⁻⁶					
	<p>Premutation</p> <ul style="list-style-type: none"> • One-third of men over age 50 with a premutation will develop problems with: <ul style="list-style-type: none"> - Balance - Memory - Tremors 	<p>Full mutation (FXS)</p> <ul style="list-style-type: none"> • Intellectual disability • Loose connective tissue • Distinctive facial features • Autism • Behavioral issues 		<p>Premutation</p> <ul style="list-style-type: none"> • 5% to 10% of women over age 50 with a premutation will develop problems with: <ul style="list-style-type: none"> - Balance - Memory - Tremors • 20% of women with a premutation may experience: <ul style="list-style-type: none"> - Early menopause - Fertility problems • Thyroid issues • Muscle pain 	<p>Full mutation (FXS)</p> <ul style="list-style-type: none"> • Mild to borderline intellectual disability • Shyness and anxiety

(Source: Barry, 2017)

e. Other Names for This Condition

- Sindrom fra (X)
- Sindrom FRAXA
- FXS
- Sindrom marker X
- Sindrom Martin-Bell
- X-linked mental retardation and macroorchidism.

Conclusion

Several genetic conditions exhibit the phenomenon of genetic anticipation. Anticipation is a phenomenon by which genetic disorders are passed on to the next generation. General anticipation occurs in trinucleotide repeat disorders, such as Huntington's disease and Myotonic dystrophy, where does it occur? dynamic mutations in DNA. Anticipation usually occurs with abnormalities caused by an unusual type of mutation called trinucleotide re-extension.

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