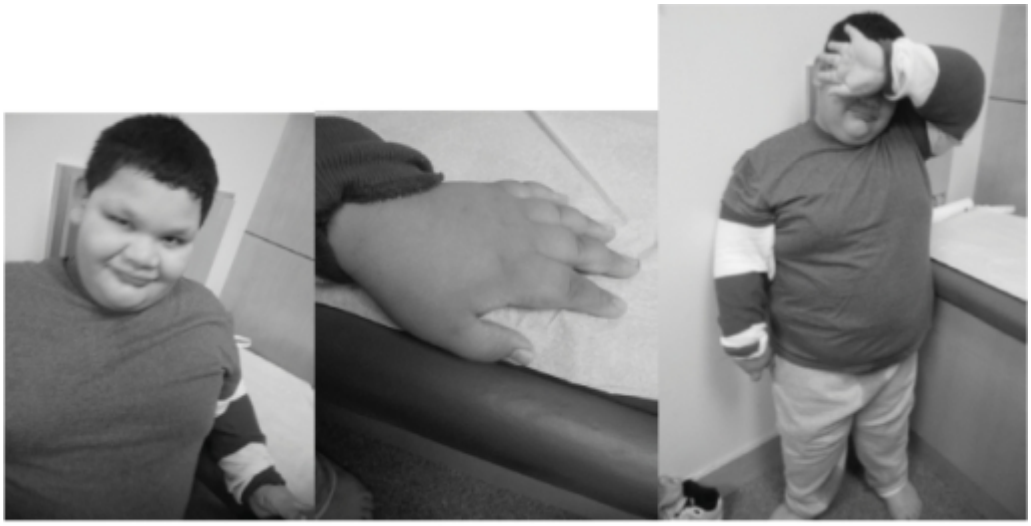
Single Gene Disorders: Fragile X Syndrome (FXS, Martin-Bell Syndrome) — CGG Expanding Repeat

See online here

Single gene disorders are caused by defects in a single gene. Although they are rare, they affect approximately 1% of the population. These can be dominant, recessive or X-linked. On the other hand, trinucleotide repeat or CGG expanding repeat disorders are characterized by the repetition of the trinucleotide sequence in certain genes leading to gene defects and disorders. Examples of trinucleotide repeat disorders include Fragile X syndrome, Huntington's disorder, and Spinocerebellar ataxia.



Single Gene Disorders

Disorders that are caused as a result of DNA alterations in one specific gene are defined as single-gene disorders. Single genes disorders are caused by a mutation of a single gene with very little influence from other genes. They show single patterns of inherited genes dominated by Mendelian laws.

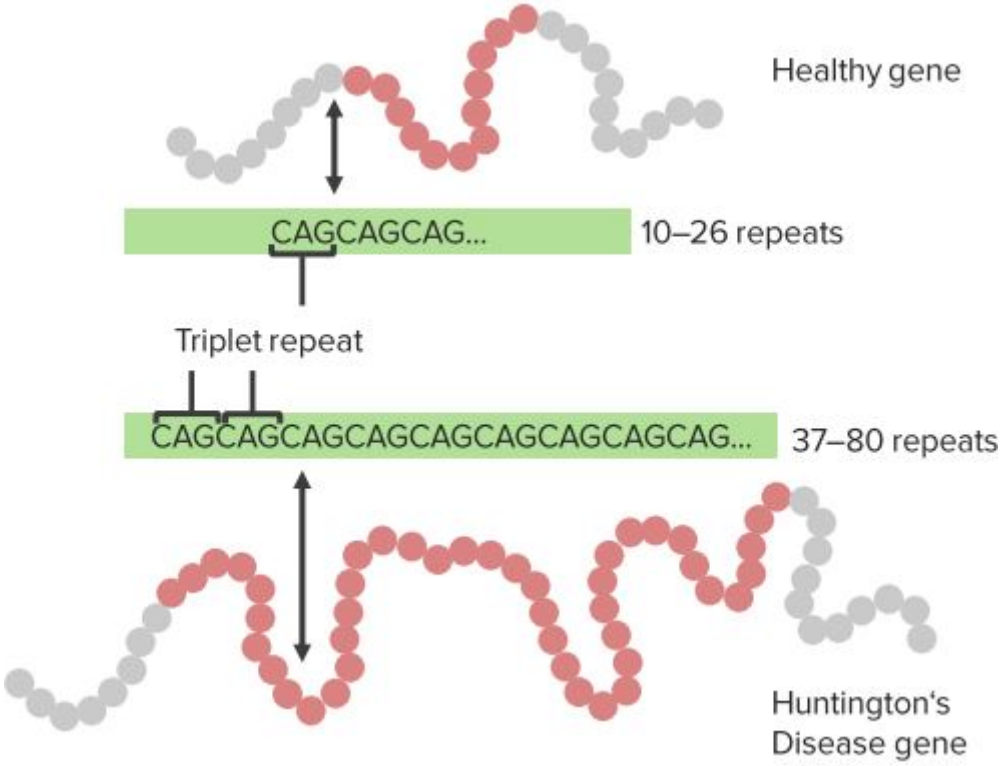
These constitute approximately 1% of the general population. It is easy to detect these disorders, track their inheritance through the generations of the same family and one can also predict the risk of their inheritance as only one single gene is responsible.

Although a single gene causes these conditions, they can also be caused by different mutations leading to varying phenotypic manifestations and severity due to variations in the individual's environment and other genetic variations. Single gene disorders can be classified as dominant, recessive or X-linked and can be diagnosed with genetic tests.

Dominant disorders e.g. Huntington’s disease

In these disorders, the affected individual inherits one mutant gene and one normal gene and is therefore heterozygous. As these copies of defective genes occur in autosomes, the inheritance is equally present in males and females. As the mutant gene is dominant over the normal gene, clinical manifestations of the disease are observed in every generation of the family and transmitted from parent to their progeny during pregnancy with 50% chances.

If an individual inherits two copies of the mutant gene, they are considered “homozygous” and have more severe manifestations of the disorder.



“Huntington´s Disease” Image created by Lecturio

Recessive disorders e.g. Sickle cell disease

The manifestations of the disorder are observed only when an individual inherits two copies of the mutant genes i.e. homozygous. The presence of a single healthy gene is sufficient to mask the effects of the mutant gene, but, if both genes are abnormal, then symptoms of the disease appear. Recessive disorders are likely to occur in consanguineous relationships i.e. if the parents are related. The chances of inheritance of this defective gene are 25% during pregnancy when both the parents are carriers of the mutated gene.

They are more difficult to detect as their features may not be manifested and, as a result, they may appear in a genealogical tree to have skipped a generation.

X-linked disorders e.g. Hemophilia

These are single-gene disorders that occur due to the mutant gene being located on the

X chromosome and can be inherited in either dominant or recessive pattern. Hemophilia and Duchenne's muscular dystrophy are examples of an X-linked recessive disorder that are seen more frequently in males. The mutant gene is passed by the mother to her male progeny who manifests the clinical features of the condition.

Women, who are carriers of the mutant gene, develop symptoms only if they have an associated chromosomal disorder or their other X chromosome is inactivated. In other words, women are carriers of the defective gene and males suffer from the condition.

X-linked dominant single-gene disorders are rare. e.g. Rett syndrome, and have identical incidence in males as well as females. Here, women exhibit 50% chances to affect her daughter or a son during each pregnancy. Men with X dominated mutated genes transmit the condition to their daughters instead of their sons.

Trinucleotide Repeat Expansions (TRE)

Several human disorders are caused by trinucleotide repeat expansion which occurs in various cells and is dependent on the gender of the parent transmitting the mutation. There are almost 14 disorders that have been reported due to TRE. Out of 4, 6 disorders are unlike each other, while 8 disorders share the identical codon, CAG, as their underlying cause. CAG codes for the amino acid, glutamine and hence these disorders are called 'polyglutamine diseases'.

However, these repeats are located on different chromosomes and hence the 8 diseases are different, although their major clinical manifestations are similar – progressive neurological degeneration beginning in mid-life or early adulthood. Examples of these 8 disorders are Huntington's disease, Spinobulbar muscular atrophy, and Spinocerebellar ataxia type 1 to type 7.

The non-polyglutamine trinucleotide repeat disorders include Fragile X syndrome, Fragile XE mental retardation, Friedrich's ataxia, Myotonic dystrophy, Spinocerebellar ataxia type 8 and type 12.

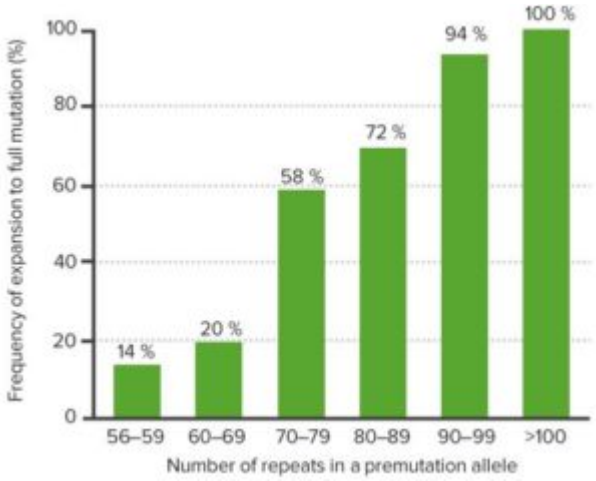
Huntington's Disease

Huntington's disease is a neurodegenerative disease caused by a polyglutamine trinucleotide repeat expansion disorder due to CAG repeats. It affects brain nerve cells by damaging them. The brain damage gets worse over time. The onset of symptoms typically starts between the age of 30 and 50 years of men and women being equally affected. The clinical manifestations of the disease can be classified as movement disorders, cognitive and psychiatric features.

The cognitive symptoms include difficulty learning anything new, communication difficulties, problems with multi-tasking, planning, and the inability to perceive space with respect to tables and walls. Involuntary movements are uncoordinated and jerky in nature. Movement symptoms include tics, muscle spasms, rigidity, dysarthrias, dysphagia, chorea, and athetosis. Increased irritability, obsessive traits like repeated hand washing, anxiety, apathy, personality changes, mania, and delirium constitute psychiatric symptoms.

Fragile X Syndrome

This is a non-polyglutamine trinucleotide repeat expansion disorder involving the CGG codon which causes moderate intellectual disability and is considered to be an autism spectrum disorder. Excessive methylation of cytosine within the FMR1 promoter region leads to condensation of the chromatin with resultant gene silencing. The FMR1 gene is located on the X chromosome and therefore provided the name of the condition. It exhibits a dominant pattern in X chromosomes.



"Fragile X Syndrome. A CGG Expanding Repeat" Image created by Lecturio

Affected individuals can have more than 200 and up to 1000 repeats while asymptomatic individuals have between 53 to 230 CGG copies. Clinical features of the syndrome include long, prominent pinnae, mental retardation, stereotypical movements of the hands and hyperactivity.

It typically affects males. Males transmit the defective mutated genes to their daughters, not their sons. A carrier mother has increased the risk of affected offspring.

Mitochondrial Disorders

These are disorders that are inherited from the mother as the mitochondria are part of the ovum during fertilization. A father who has a mitochondrial mutation cannot transmit the mutation to his progeny. The mitochondria have their own DNA which mutates at a rate greater than 20 times that of nuclear DNA.

Inheritance of mitochondrial disorders includes autosomal dominant, autosomal recessive and X-linked recessive. They can affect different organ systems; their onset can be at any age, and they affect males and females equally. Their phenotypic expression can differ in individuals of the same family and depends on the type of mutation, the prevalence of mutant mitochondria (whether homoplasmy or heteroplasmy) and the organ which is involved.

Carriers of the mutated genes through mitochondria do not suffer from the condition, they transmit their genes to their offspring; out of which, 25% are in the disease condition, 50% are carriers and the rest (25%) do not exhibit either the condition or carrier trait.

Examples of mitochondrial disorders include Leber optic atrophy and MERRF syndrome.

References

Appendix GSingle-Gene Disorders via ncbi.nlm.nih.gov

What are single gene disorders? via yourgenome.org

Single Gene Disorders via hihg.med.miami.edu

Trinucleotide Repeat Disorders via http://web.stanford.edu

Mechanisms of trinucleotide repeat instability during human development via ncbi.nlm.nih.gov

Mitochondrial inheritance via utmb.edu

Notes