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Research Article

Basic Understanding Anticipation Gene, Lead to Manifestation Oral Disease: A Review Article.

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Abstract

Introduction: Anticipation of genes in genetics is a phenomenon that genetic disorders are passed from one generation to the next. The symptoms of this genetic disorder become clearer with early age with each generation. In many cases, the increase in symptom severity also occurs in later generations. Gene anticipation is common in diseases with trinucleotide repetition disorders, such as Huntington's disease and myotonic dystrophy. This disease occurs quite dynamic mutase in DNA. All of these diseases also have neurological symptoms. Anticipation of genes is still debated, including biological phenomena or earlier diagnosis related to increased awareness of disease symptoms in the family. There are two disease manifestation related oral disease, such as hutington and bechet disease. This article aims to review basic understanding anticipation gene, lead to manifestation oral disease.

Discussion: Genetic anticipation is the phenomenon of an earlier age of onset or an increase in the severity of the clinical picture of genetic disorders as they are passed on to the next generation. The molecular mechanisms underlying anticipation are largely unknown but are typically associated with repeated trinucleotide expansions in several genetic diseases. In cancer, genetic anticipation has previously been described in several hereditary cancer syndromes, such as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), leukemia, Li-Fraumeni Syndrome and also in breast and ovarian cancer. Evidence suggests that short telomeres and subsequent genomic instability contribute to the anticipation of malignant transformation genes. Telomere shortening has been described as a genetic anticipatory mechanism in congenital dyskeratosis and Li-Fraumeni syndrome. Women who carry mutations in the BRCA1 or BRCA2 genes, and part of the BRCAX family, are characterized by short telomeres. In this case, genetic anticipation, successive cancer baseline age, in this family was associated with a decrease in telomere length in the affected girls compared to their mothers.

Conclusion: Huntington's disease shows anticipation and expansion of repeated CAG trips. All repeat triplets in genetic diseases identified to date show anticipation. Several other diseases also show anticipation including spinocerebellar ataxia type 2, bipolar affective disorder, Bechet's syndrome and spastic heratitis paraparesis (Strumpell's disease).

Keywords: Anticipation Gene; Mutation; Oral disease; Bechet; Hutington

Introduction

Anticipation of genes in genetics is a phenomenon that genetic disorders are passed from one generation to the next. The symptoms of this genetic disorder become clearer with early age with each generation. In many cases, the increase in symptom severity also occurs in later generations. Gene anticipation is common in diseases with trinucleotide repetition disorders, such as Huntington's disease and myotonic dystrophy. This disease occurs quite dynamic

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mutase in DNA. All of these diseases also have neurological symptoms. Anticipation of genes is still debated, including biological phenomena or earlier diagnosis related to increased awareness of disease symptoms in the family [1]. Anticipation usually occurs with abnormalities caused by an unusual type of mutation called trinucleotide re-expansion. A trinucleotide repeat is a sequence of three blocks of DNA (nucleotide) that repeat several times in a row. 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 genes are passed from parent to child. If the number of repetitions increases, this can be known as the trinucleotide repeating expansion. In some cases, expansion of trinucleotide repeats can occur until the genes stop functioning normally but may also cause some abnormalities to become more severe with each successive generation [2]. In the past 3 years, the molecular basis of 10 human genetic disorders, including X syndrome (FRAXA and FRAXE), Myotonic Dystrophy (DM), Kennedy disease, Huntington's disease (HD), type 1 spinocerebellar ataxia (SCA1), and dentatorubral-pallidoluysian atrophy included in the anticipation of genes. The disease is characterized at the molecular level by simple triplet repeat expansion (CTG and CGG) from less than 15 copies in normal individuals to the number of copies in affected cases. Thousands of copies were found in some X cases and myotonic dystrophy. This increase in size occurs after the transmission of extended repeats on the chromosomes of the offspring. Repetition instability in the genome is also associated with hereditary nonpolipotic colon cancer, which may involve mutations in repair function [3]. There are two disease manifestation related oral disease, such as hutington and bechet disease. This article aims to review basic understanding anticipation gene, lead to manifestation oral disease.

Discussion

Genetic anticipation is the phenomenon of an earlier age of onset or an increase in the severity of the clinical picture of genetic disorders as they are passed on to the next generation. The molecular mechanisms underlying anticipation are largely unknown but are typically associated with repeated trinucleotide expansions in several genetic diseases. In cancer, genetic anticipation has previously been described in several hereditary cancer syndromes, such as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), leukemia, Li-Fraumeni Syndrome and also in breast and ovarian cancer [4]. Evidence suggests that short telomeres and subsequent genomic instability contribute to the anticipation of malignant transformation genes. Telomere shortening has been described as a genetic anticipatory mechanism in congenital dyskeratosis and Li-Fraumeni syndrome. Women who carry mutations in the BRCA1 or BRCA2 genes, and part of the BRCAX family, are characterized by short telomeres. In this case, genetic anticipation, successive cancer baseline age, in this family was associated with a decrease in telomere length in the affected girls compared to their mothers [5]. Telomere shortening has recently been described as another mechanism of anticipation, associated with early onset and severity of disease in genetic disorders, such as dyskeratosis congenita, a disease characterized by skin disorders, bone marrow failure and an increased predisposition to cancer, and in Li - Fraumeni Syndrome. Families with congenital dyskeratosis have mutations in genes in the telomerase or shelterin complexes, which cause reduced telomerase activity. Telomeres are nucleoprotein structures that protect the ends of chromosomes. Telomeres are shortening each cell cycle and there is increasing evidence to suggest that short telomeres and subsequent genomic instability contribute to malignant transformations. Telomere dysfunction appears to underlie the development of many genetic, degenerative, aging and cancer diseases. Our results suggest that short telomeres in peripheral blood cells are characteristic of hereditary breast cancer patients and that telomere shortening often occurs with successive generations in this family, suggesting that telomere shortening could be a mechanism to explain the phenomenon of anticipation of age in this disease [6].

Mechanism Anticipation Gene

Trinucleotide repetitions seen at a number of loci in the human genome are found in introns, exons and 5'or 3' UTR's. This loop consists of a three-nucleotide pattern (e.g., CGG) that repeats itself several times. During meiosis, an unstable loop can undergo triplet expansion. Germ and prokaryote cells can occur and produce a greater number of repetitions than those found in somatic tissue. The mechanism behind triplet loop expansion is not well understood. One hypothesis is that an increase in the number of repetitions affects the overall shape of DNA, which could affect interactions with DNA polymerase and thus affect genes [7]. At some loci, trinucleotide expansion is harmless. However, at some other loci expansion has an adverse effect causing symptoms. When the trinucleotide repeats are within the protein coding region, the repeated expansion results in the production of protein mutases without any function or function that is not supposed to be. An example is the case of Huntington's disease, in which a trinucleotide repeat encodes a long glutamine residue. Other cases that affect gene expression where repetition is found in fragile X or several genes so that a dominant negative effect occurs, for example in the case of Myotonic dystrophy [8]. The bad effect will occur if the number of repetitions has passed a certain limit. For example, normal individuals have between 5 and 30 repetitions of CTG in 3'UTR DMPK, a gene altered in myotonic dystrophy. If the number of repetitions becomes more than 50, the person is only slightly affected-perhaps only having cataracts. However, meiotic instability can lead to dynamic mutations that increase the number of repetitions in the offspring that inherit the mutant allele. Once the number of repetitions reaches more than 100, the disease will

occur earlier or later in life (although the individual will still reach adulthood before symptoms become apparent) and the symptoms will be more severe-including myotonia. As the number increases above 400, the symptoms show themselves in childhood or in infancy [9].

The concept that must be considered in the gene anticipation mechanism is 6, first is the type of template sequence plays a major role, and CGG being the most unstable. Second, the length of the repetitions is very important because longer counts, especially for CGG, show a greater degree of instability compared to shorter increments (30 or less). Third, the reduction greatly increases the stability of the triplet loop, especially for CGG. Alleles derived from human patients showed stable and unstable CGG triplets of the same size, suggesting that features other than length, but intrinsically repeatable, are responsible for stability. CGG lengths greater than 33 that are not disturbed indicate instability, and loss of AGG is a major mutation in the generation of alleles prone to syndrome X. Fourth, the orientation of the addition relative to the origin of replication can also influence gene anticipation. Fifth, the location of addition depends on the DNA polymerase. Sixth, the number of copies of genes is the main cause of gene anticipation. Expansion formation provides the concept that mutations are DNA itself or that its structure is mutagenic [10].

Expansion (Repetition) and Deletion in Anticipation of Genes

In some literature, the anticipation of genes can be expansion and deletion, although there is more expansion. The large expansion occurs when the CTGs are on the leading template strand. Whereas deletion occurs when the CTG is in the opposite order. Genetic instability can occur if expansion by CTG and CAG DNA is single sequential. The structure that changes occurs due to repetition. For expansion, a loop can form on the new DNA strand that is left behind (the CTG strand). CTG oligomers form stable anti-parallel duplexes with TT pairs, whereas complementary CAG strands form metastable [11]. The deletion mechanism occurs when CTG is a trailing strand template, a loop can form on the trailing strand which will be skipped during DNA synthesis to produce deletion. Some of the losses can occur by the polymerase enzyme caused by the DNA structure or the presence of proteins. Further processing can lose continuously (primary use) of a larger sequence. Recently it was found that the CTG and CGG duplexes had abnormal properties including nucleosome formation, causing DNA polymerase to stop, as well as helical looping and polyacrylamide gel migration. Deletions only occur on CTG, not in DNA that is repeated. Many of the products of the deletion are heterogeneous, about 140, 100, 60, and 20 repetitions. DNA structure A glimpse of the sequence re-sequences in plasmids adopting a non-B conformation under appropriate conditions [11]. The nucleosome is the basic structural element of chromosomes and consists of 146 bp of DNA which is attached to histone proteins which mediate general transcription repression. Plasmids containing CTG lengths from 0 to 250 repetitions were investigated. The efficiency of nucleosome formation is increased with the extended triplet block which indicates that the block can suppress transcription through stable nucleus formation. In fact, the extended CTG triplet repeat is the most powerful known element of nucleosome position, even compared to genes, one of the most powerful natural nucleosome position sequences. RNA polymerase moves from right to left along the DNA molecule, releasing it and writing the code into mRNA. Short triplet repetitions are unobtrusive because the nucleosomes move when the polymerase attacks them. This movement is called "Nucleosome Transfer." The extended loop is long, inhibiting nucleosome transfer as they form unusually strong DNA histone contacts. When the polymerase stops, the accumulation of mRNA transcripts will stop [12].

Anticipation Gene Related to Oral Disease

Huntington's disease shows anticipation and expansion of repeated CAG trips (1, 2, 3, 4, 5, 10). Repeats of CAG between 11 and 34bp in the normal population encode polyglutamine in the IT15 gene. An expansion of about 90bp occurs in HD patients. Age of onset correlated with repetitive triplet length with the greatest change in repetitive range seen in paternal transmission. The intermediate allele, IA, containing 30-38 (or 34-38) repeats possibly similar to premedication on X or DM [13]. Given Mendel's genetic principles, gene anticipation is a puzzle. The discovery of widespread triplet repeats or mutations in diseases that suggest anticipation provides a physical basis for genetic phenomena. Expansion of triplet repeats results in genetic defects, which affect the activity of glutamine-containing proteins (SBMA, HD, SCA1, and DRPLA) or affect the level of expression of genes associated with repetition (X and DM). All repeat triplets in genetic diseases identified to date show anticipation. Several other diseases also show anticipation including spinocerebellar ataxia type 2, bipolar affective disorder, Bechet's syndrome and spastic heratitis paraparesis (Strumpell's disease). If there is an association between anticipation and triplet repetition, more diseases that show anticipation can be identified because there are more than 40 genes that contain repetitive triplet genes [14]. Several other diseases that show manifestations of gene anticipation include [15] Table 1.

Table 1: Anticipation Gene Related to Oral Disease.

Autosomal Dominant	Autosomal Recessive
Multiple spinocerebellar ataxias	Friedreich's ataxia - GAA
Huntington's disease - CAG	X-linked
Myotonic dystrophy - CTG	Fragile X Syndrome - CGG
Congenital dyskeratosis-TTAGGG (telomere repeating sequence)	No expression type
	Crohn's disease
	Behçet's disease

Conclusion

Huntington's disease shows anticipation and expansion of repeated CAG trips. All repeat triplets in genetic diseases identified to date show anticipation. Several other diseases also show anticipation including spinocerebellar ataxia type 2, bipolar affective disorder, Bechet's syndrome and spastic heratitis paraparesis (Strumpell's disease).

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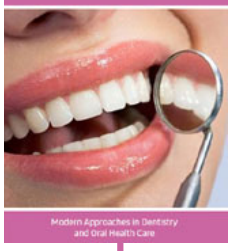

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