MCB 142 Discussion

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1 Announcements

The midterm exams are being graded by readers. The answer key will be made available after exams are returned.

2 Understanding Mutations

2.1 Huntington's Disease

The gene for Huntington's disease codes for a protein called huntingtin. The mutation associated with the disease involves expansion of a CAG triplet repeat sequence in the coding region of the gene.

Do you expect the mutation to be dominant or recessive? Gain of function or loss of function? Why?

Variation in the length of the tandem repeat sequence seems to correlate with age of onset. Individuals with longer repeat alleles are often found to develop the disease at an earlier age. What's a possible hypothesis to explain this trend?

2.2 Retinoblastoma

The hereditary form of retinoblastoma is caused by mutations that affect the RB1 gene, a tumor suppressor. The mutations can involve chromosomal deletions, nonsense mutations or frameshift mutations.

Do you expect the mutation to be gain of function or loss of function? Why?

Although you need two mutated copies of RB1 to develop a tumors, most of the individuals with retinoblastoma are heterozygous for the mutation. What's a possible explanation?

2.3 Tay-Sachs Disease

Tay-Sachs disease is a well-known autosomal recessive disorder. Some common mutations that cause the disease include:

- 4 base pair insertion in an exon that introduces a premature stop codon

- single base transversion in the splice site of an intron
- 7.6 kilobase deletion starting upstream of the promoter region and ending in the first intron
- single base transition that results in a change in amino acid from glutamate to lysine

How would you describe each of these mutations, and how do they lead to loss of function?

2.4 Cystic Fibrosis

Cystic fibrosis is another well-known autosomal recessive disorder. The most common mutation that causes the disease is a deletion of three base pairs in an exon that leads to the absence of phenylalanine in the translated protein. However, there are other mutations that can cause the disease. Researchers have classfied these alleles into six classes depending on their effect on phenotype:

- defective protein production
- defective protein processing
- defective protein regulation
- defective protein conductance
- reduced amounts of functional protein
- reduced protein stability

What sort of mutations can lead to these different types of loss of function? How can different combinations of disease alleles explain differences in penetrance and expressivity?

3 Experimental Genetics

As Prof. Dernburg begins to discuss how genetics can be used as a tool for understanding biological processes, here are some of the common genetic techniques we will be discussing:

- screens
- selections
- mutagenesis
- complementation tests
- epistatic analysis
- mosaics