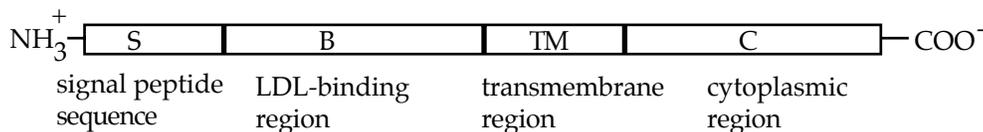


7.012 Section problem: FH and LDL receptors

Familial Hypercholesterolemia (FH) is characterized by an increased level of low density lipoprotein (LDL) in the blood. The primary cause of FH is a non-functional LDL receptor protein (LDL-R) that results in decreased or no uptake of LDL particles containing cholesterol into cells. First, LDL on the outside of the cell binds to the LDL receptor; next, the LDL-LDLR complex undergoes endocytosis into a vesicle; finally, the cholesterol is released into the cell.

a) Two forms, a mild and a severe form, are seen among individuals affected with FH. What is the simplest genetic explanation for the two forms of FH?

b) The LDL-R protein, shown below, consists of: a signal peptide sequence (S) which is cleaved during translation, a transmembrane region (TM) which inserts the receptor in the membrane; a ligand-binding region (B) which binds LDL, and a cytoplasmic region (C) which is necessary for internalization.



Mutations in any of these regions can lead to the production of non-functional receptors. Given the above information, indicate which region of the receptor protein could be defective in each individual **and** why it would cause the effects described. (You may assume that altering one region leaves the others unaffected.)

i) Individual homozygous for mutation #1 in LDL-R gene: The LDL-R is not in the plasma membrane, but is secreted outside the cells.

ii) Individual homozygous for mutation #2 in LDL receptor gene: The LDL-R is in the plasma membrane and binds LDL but the complex is not internalized.

iii) Individual homozygous for mutation #3 in LDL-R gene: The LDL-R is not in the plasma membrane, but is found in the cytoplasm.

iv) Individual homozygous for mutation #4 in LDL-R gene: The LDL-R is not in the plasma membrane, but is found in the lysosomal membrane.

c) Some types of drug treatments for FH work by blocking cholesterol synthesis in liver cells which subsequently leads to increased transcription of the LDL receptor gene in these cells and the lowering of blood LDL levels. Why might this type of drug therapy be effective when taken by individuals with the mild form of FH whereas it is not effective for individuals with the severe form of FH?