

## 7.012 Section on FH and LDL receptors- Solutions

a) Although FH exhibits an autosomal recessive mode of inheritance, the lack of one functional copy of the wild-type LDL-R gene as in FH heterozygotes leads to a 50% reduction in the uptake of LDL from blood. The FH homozygotes, with the severe form of FH, have two copies of the mutant LDL-R allele, and thus no functional LDL-R protein.

b)

i) The transmembrane region of the receptor is defective; therefore, the receptor cannot be inserted (anchored) in the membrane and is secreted outside the cell.

ii) The cytoplasmic portion of the receptor is defective; therefore, the LDL-LDL-R complex cannot be internalized into the cell.

iii) The signal peptide sequence is defective; therefore, the protein is not translocated to the ER membrane and is found in the cytosol in the cell.

iv) An aberrant trafficking signal may have been attached or arisen by mutation in the coding sequence so that it is sent to the lysosome instead of fusing to the plasma membrane.

c) The drugs when taken by individuals with the mild form of FH (the heterozygotes) work by increasing the rate of transcription of their one wt copy of the LDL-receptor (LDL-R) gene, thus increasing the total amount of functional LDL-receptor in the liver cell. This results in an increase in the rate at which the liver takes up low-density lipoprotein (LDL) that leads to a lowering of blood LDL levels. Although the drug also blocks cholesterol synthesis in individuals with the more severe form of FH (the FH homozygotes), it does not reduce their blood LDL levels because their liver is not capable of making any functional LDL-receptors (they do not have any wt copies of the LDL-R gene).

d) This FH homozygote most likely has a mutation in the LDL-receptor gene such that their cells can bind LDL, but the cells cannot internalize the LDL-receptor complex.