This assignment is due on Fri May 21 at 11:30AM.

ABSOLUTELY NO ASSIGNMENTS WILL BE ACCEPTED AFTER THIS DEADLINE

Please read carefully through this quiz before Monday May 17. I will answer questions about it in class. I can’t take questions during office hours since I want the entire class to have access to the same information (from me). You can email me questions but I will only address them during class.

Rules for working this quiz: This is an open-note, open-book, open-internet quiz. You may discuss these questions with your fellow classmates but, you MUST write up your answers independently. In other words, if any answers look suspiciously similar I will divide the total possible points between the similar answers. Also please do not consult other faculty members about the quiz.

If I can’t easily read your answers, I will not grade them.

If you choose this option, print out the following pages and put your answers to 1a-d and 2a-b directly on the quiz. Attach an extra sheet of paper with your answers to 1e and 2c.
Option 2 Question 1 (16 pts)  A mutation has been identified in the gene coding for the following polypeptide. The mutant polypeptide results from a single base pair addition, deletion or substitution.

Wild-type: ..... lys asn trp arg met lys* met met arg
Mutant: ........ lys asn trp arg ile* lys*

a. What is the general type of mutation at the protein level?  frameshift

b. Why is the polypeptide is shorter than wild-type?(one sentence) the shift in reading frame results in a stop codon that truncates the polypeptide

c. Indicate the codons specifying the starred amino acids. Both lysines are AAA  Isoleucine: AUA

d. What general class of mutagens could have caused this mutation? One sentence. Intercalating agents cause the addition or deletion of one or a few base pairs

e. For the wildtype allele, write out the sequence (both DNA strands) coding for the portion of the polypeptide shown and show the location and nature of the mutation. Label the strand that RNA polymerase uses as a template.

- If there are codon ambiguities, indicate with the following standard code:  N = aNy base
  R= puRine     Y= pYrimidine
- Be sure to label all 5’ and 3’ ends
- Don’t forget to label the strand that RNA polymerase uses as a template.
- Note, you don’t need to show me how the mutation came about – just where it is in the sequence that you have written out

5’ AAR AAY TGG C/AGN ATG[AAA ATG ATG C/AGN 3’
3’ TTY TTR ACC G/TCN TAC[TTT TAC TAC G/TCN

BOTTOM STRAND SERVES AT THE TEMPLATE FOR RNA POLYMERASE
BOXED GC IS DELETED IN THE MUTANT ALLELE
**Option 2 Question 2. (14 pts)** Huntington disease (HD) is caused by a variable expressed but fully penetrant autosomal dominant mutation that causes late onset (post-reproductive) neurodegeneration. The mutations that cause HD involve an expansion of a triplet repeat located in the coding region of the gene (HTT --see underlined sequence below). Normal alleles of this gene have 27-35 CAG repeats. Alleles with >40 repeats confer a clear HD phenotype. Interestingly, as the number of repeated triplets increases, the age of onset in the patient decreases. Furthermore, because the unstable trinucleotide repeat can lengthen when passed from parent to child, the age of onset can decrease from one generation to the next.

**Homo sapiens huntingtin (HTT), mRNA (in cDNA language)**

>gi|90903230|ref|NM_002111.6| Homo sapiens huntingtin (HTT), mRNA

GCTGCCGGGACGGTCCAAAGATGAAGACGCCGCTAGTTCTGCTTTTACCTCGGCCCAGAGCCCCATTC
ATTGCCCGCTGCTGAGCCGCGGATGCTGGGAGGACTGCGCCCGGAGGCCTCCGGCTGCCGGGCGGGAGAC
CCGCCGCGGGGACGGGTTCTGCTTTTACCTCGGCCCAGAGCCCCATTC

**a.** The beginning of the *huntingtin* mRNA is shown above. **Circle the translation start codon.**

*NOTE – credit given for circling any one of the ATGs that are in red above –due to the complication described on the next page.***

**b.** Will an expansion or contraction of the number of CAG repeats result in a **frameshift** at the protein level: **Circle NO**

*One sentence defense of your answer (no credit if no explanation):*

*Since the sequence is read in multiples of three, deleting or adding three contiguous bases deletes or adds amino acids but does not change the reading frame.*

**c.** **ATTACH** a clearly labelled diagram to show how an increase of one CAG repeat unit can occur as a spontaneous mistake during DNA replication:

- Be sure to label the 5’ and 3’ ends of all DNA strands.
- Be sure to label the parental and daughter DNA strands for every round of replication.
- **Start with the sequence shown below and but only track relevant parts of sequence**
- **Hint: the initial mistake can occur during the replication of either parental strand so follow the replication of just one of the parentals and be sure to end up with the extra repeat unit in both strands**

5’----------------- CTCAAGTCCTTCCAGCAGCAGCAG ----------------3’
3’----------------- GAGTTCAAGGAGGTCGTGTCGTGTC ----------------5’

The initial mistake is caused by slippage of the 3’ end of the daughter strand during replication. The realignment of the template/daughter strand causes a loop of one repeat unit in the daughter strand and after completion of DNA synthesis, a net addition of one repeat unit.
Typically translation in euks starts at the first AUG, but sequence context can be important, and for the HTT mRNA, translation starts at the second AUG (see forward frame 2 in figure below) because its sequence context matches the vertebrate consensus for defining a starter AUG. Note the first ATG below is a partial match to the consensus and the second is almost an exact match. The third ATG (in same reading frame as the second ATG) does not match at all. By definition of consensus, the sequence context doesn’t have to exactly match the consensus to function OK. BUT, if the first ATG set the reading frame, we would have a problem because there is an in-frame stop codon several codons later – see forward frame 3 in diagram below.

**Homo sapiens huntingtin (HTT), mRNA (in cDNA language)**

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>gi|90903230|ref|NM_002111.6| Homo sapiens huntingtin (HTT), mRNA
GCTGCCGGGACGGGTCCA
      ATG
AG
ACGGCCGCTCAGGTTCTGTTTACTCTGGGCCAGACAGCCCCATTC
ATTGCCCGTGCTGAGCGGCAGCCGAGCTCGCCGAGGGACTGCCGTGCCGGGCGGGAGACC GCCCATGGCGACCCCTGGAAGCACTAGTAAGGCTTCTAGCCATCTCCACAGGCACAGAGAG
GCAGACCAGACAGCACGACGCACGACGCACGACGACGACGACGACGACGACGACGACGACGACGACG
CGGCCGCCGCCGCCCTTCAGGGCTCTCTCCAGGGCAGGGCGAGGGCGAGGGCGAGGGCGAGGGCGAGGG
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**huntingtin [Homo sapiens]**

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>gi|90903231|ref|NP_002102.4| huntingtin [Homo sapiens]
MATLEKLMKAFESLKSFQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQ