Rieder - Genetics
Worksheet 3
Due: 9/26/17 at the beginning of class

Name: _____

About how long did this homework take you? _____

I consulted/worked with: _____

I will not accept late homework. Special exceptions will be made **only** in the event of illness or if you contact me at least 24 hours ahead of when the assignment is due (at my discretion).

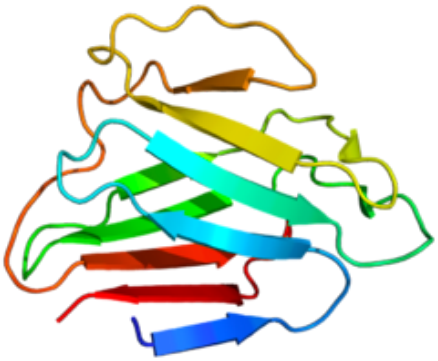
POINTS: / 50

For this homework, please read the remarkable Propublica story about Jill Viles and Priscilla Lopes-Schliep: "The DIY Scientist, the Olympian, and the Mutated Gene."
If you enjoyed this story as much as I did, you can also listen to the author, David Epstein, on This American Life: Something Only I Can See/Act 1: Do these genes make me look fatless?

In Thursday's class, we talked about Duchenne muscular dystrophy (MD), which is caused by mutations in the **dystrophin** gene. Together, we decided that Liam, who is affected by MD, has an **allele** of dystrophin that contains a **nonsense mutation,** and that this is the likely cause of his MD **phenotype** (observable traits).

Jill Viles has Emery-Dreifuss MD, which can be caused by mutations in genes besides dystrophin (there are many genetic ways to lose muscle mass!). Jill and Priscilla both have a mutation in the **lamin a/c (LMNA)** gene, which leads to different **alleles**. In both women, the LMNA mutations cause **lipodystrophy**, where the body cannot accumulate fat. However, Jill's mutation also leads to MD, while Priscilla's leads to large, pronounced muscles; almost polar opposite **phenotypes** (observable traits)!

Here is a picture of the **wild-type** (normal) version of the LMNA protein:



1. What kind of **secondary structures** do you notice in this protein (3 pts)?

2. Based on the picture, does the LMNA protein have **quaternary structure**? How do you know (3 pts)?

3. Jill says of her mutation, *"It comes down to a G that was changed to a C."* A nucleotide substitution like this is called a **point mutation**; no nucleotides are deleted or added, just substituted. Let's assume Jill's mutation is in an **intron**. Is it possible that Jill's mutation leads to a **frameshift** (3 pts)? Why/why not?

4. For this question and for all questions following, let's assume Jill's mutation is in an **exon**. Is it possible that Jill's mutation leads to a **frameshift** (3 pts)? Why/why not?

5. Do you think Jill would have the MD/lipodystrophy **phenotype** if her mutation were a **silent mutation** (3 pts)? Why/why not?

6. Is it possible that Jill's mutation (G to C point mutation) causes a **nonsense mutation** (3 pts)? Why/why not? (consult a codon table)

7. Could Jill's mutation (G to C point mutation) cause **"read through**" of a stop codon (the conversion of a stop codon into a codon that represents an amino acid) (3 pts)? Why/why not? (consult a codon table)

8. Why do you think frameshifts and nonsense mutations are more likely to cause disease **phenotypes** (symptoms) than missense mutations or silent mutations (4 pts)?

9. Jill and Priscilla's mutations are very, very close to each other in the **primary sequence** (the linear sequence of amino acids) of the LMNA protein. The entire protein is over 650 amino acids long!

Jill's mutation is called "R527P"
Priscilla's mutation is called "L530P"

- The first letter refers to the **wild-type** (normal) amino acid: "R" is *arginine*, "L" is *leucine*.
- The number refers to the amino acid's position in the protein: "527" is the five hundred twenty seventh amino acid in the LMNA protein (out of ~650), while "530" is just three amino acids later.
- The second letter refers to the amino acid that is substituted after the mutation: "P" is *proline*.

What type of mutation are R527P and L530P (they are the same type; we already know they are **point mutations**-- use a different word you have learned) (3 pts)?

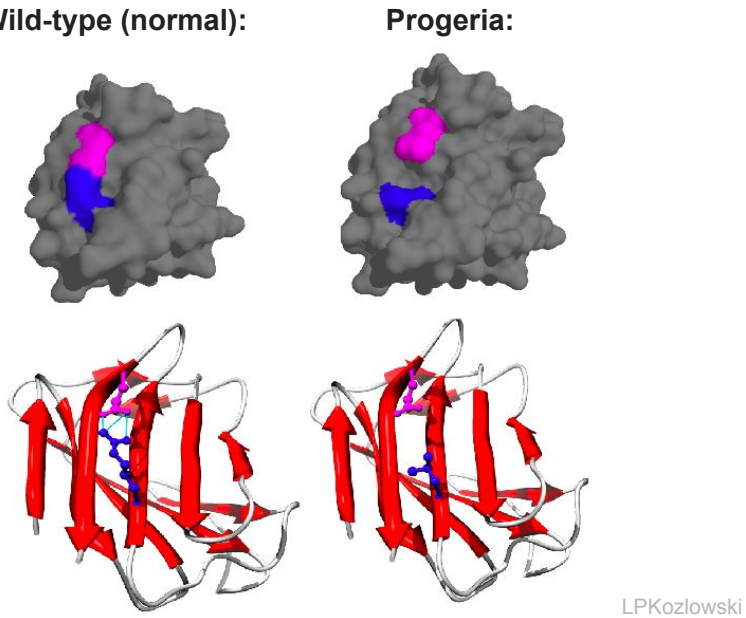
10. Think about how amino acids are classified by their chemical properties, like "polar," "nonpolar," "acidic," or "basic." We discussed this in class, but you can also just google "amino acid table" and you will see what I mean.

Do you think Jill's LMNA protein would have a better chance of functioning properly (as in not resulting in MD, not resulting in large muscles) if her mutation was R527K ("R" is arginine; "K" is *lysine*), rather than R527P (3 pts)? Why/why not?

11. Do you think Priscilla's LMNA protein would have a better chance of functioning properly (as in not resulting in large muscles, MD) if her mutation was L530S ("L" is leucine; "S" is *serine*), rather than L530P (3 pts)? Why/why not?

12. How can it be possible that two nearby mutations in the same gene (LMNA) lead Jill and Priscilla's very, very different **phenotypes** (observable traits--symptoms) (6 pts)?

Mutations in the LMNA gene can cause other disorders, for example, **progeria** syndrome, which causes premature ageing. Children with progeria are often bald and have wrinkles; you may (or may not) have heard of "Benjamin Button" syndrome (The Curious Case of Benjamin Button is a movie starring Brad Pitt that people in my age group have all heard of…).



Above are two kinds of diagrams showing both the wild-type LMNA protein and the mutated protein that can lead to progeria. The top blobby diagram is called a "space filling" diagram, while the bottom diagram shows us the **secondary** and **tertiary structures** of the proteins (similar to the picture in Question 1).

In both the **wild-type** (normal) and progeria situation, **pink** is the amino acid *glutamate* 537. In the wild-type situation, **blue** represents the amino acid arginine 527. However, in the progeria situation, there is the mutation R527L ("R" = arginine; "L" = leucine), so the **blue** amino acid now represents leucine 527 in the progeria situation. Note that amino acid 527 is the same amino acid that is mutated in Jill, who has the MD phenotype (not progeria)!

You can see that the **pink** and **blue** amino acids interact and touch in the **wild-type** (normal) situation but not in the progeria situation, and this subtly changes the shape of the entire LMNA protein.

13. Even though progeria is caused by a genetic mutation, it is inherited by children; sadly, progeria patients die during childhood before they reproduce and pass their mutations to their own children. How do you think they came to have their mutations, for example R527L, if it's not inherited from their parents (4 pts)? Your book might be a big help for this question.

14. We have discussed that although **DNA polymerase** has **3' to 5' proofreading activity**, it occasionally incorporates the incorrect nucleotide during DNA replication, leading to a mutation (about 1 per 10 billion nucleotides is erroneous due to DNA polymerase. Since there are 3 billion nucleotides in the human genome, this leads to about one mutation per 3.3 cell divisions).

What would happen if the R527L progeria mutation (a heritable change in the DNA sequence) suddenly happened tomorrow in your LMNA gene in one of your **somatic** (body) cells during DNA replication? That is, would you suddenly start to show progeria symptoms (3 pts)? Why/why not?

15. What could happen if the R527L progeria mutation occurred in your LMNA gene during DNA replication in one of your **germ** cells (that make your sperm/eggs) (3 pts)? Would you show Progeria symptoms? Who might be affected?

Extra Credit!

Unlike the LMNA mutations that lead to progeria, the LMNA mutations that lead to Emery-Dreifuss MD *are* hereditary. When Jill's story was first published, one of her greatest fears was that people would criticize her for choosing to have a child, even though she knew her child might inherit her genetic disease (there was a 50/50 chance her son would inherit her mutation. Thankfully, he did not). What are some of the ethical considerations on both sides (1 pt)?

Priscilla's mutation led to a very different **phenotype** than Jill's did. Do you think people would have criticized Priscilla if she had known about her LMNA mutation earlier and still chosen to have children (1 pt)?