Genetic Mutations and Breast Cancer, continued

Name: *Answer Key*

Partner's name: *N/A*

Homeroom: *N/A*

LO: Predict whether a mutated protein will still work.

SLE: Meet NGSS.

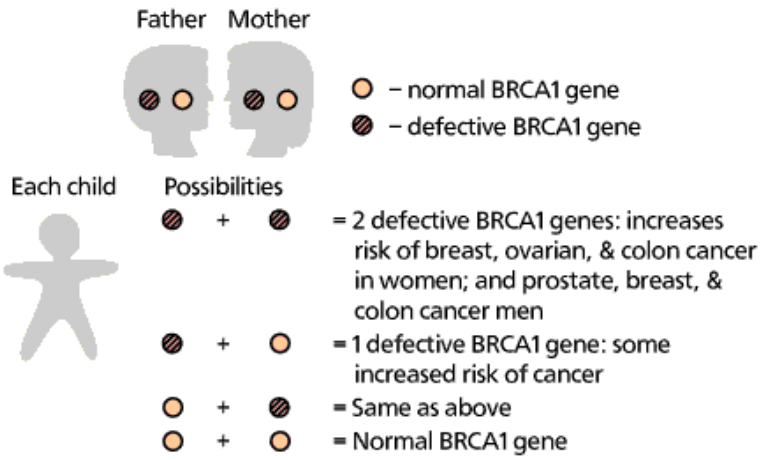


Image: history.nih.gov/exhibits/genetics/sect2.htm

Below is the grading rubric followed by the full answer key.

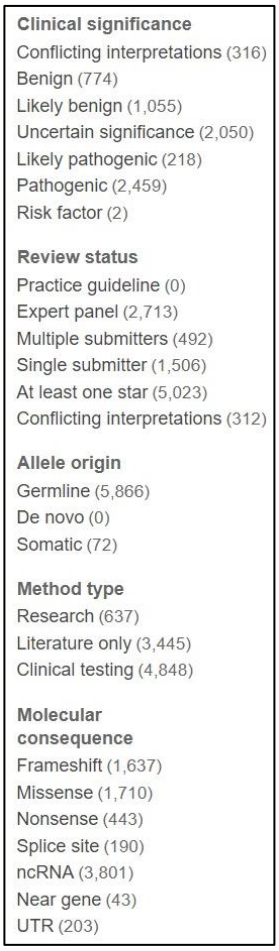
Grading Rubric

Each answer was graded in a "binary" fashion (either adequate or inadequate).

Question	0 (inadequate answer)	1 (adequate answer)
1a	Any answer other than 1635.	Correct answer (1635).
1b	Any answer other than 1466.	Correct answer (1466).
1c	Incorrect calculation.	Percentage correctly calculated from answers to 1a and 1b (90%, if 1a and 1b were correct).
2a	Any answer other than 1710.	Correct answer (1710).
2b	Any answer other than 79.	Correct answer (79).
2c	Incorrect calculation.	Percentage correctly calculated from answers to 2a and 2b (5%, if 2a and 2b were correct).
3	Incorrect conclusion based on answers to 1c and 2c.	Conclusion that frameshift mutations are more often pathogenic if answer to 1c was higher than answer to 2c, or conclusion that substitution mutations are more often pathogenic if 2c > 1c.
4	Answer does not apply 1a-2c to BRCA2.	Answer applies the processes of questions 1a-2c to BRCA2.
5	Answer of "yes," or answer of "no" without logical explanation.	Explanation that the relationship between RNA bases and amino acids does not change.
6a	Illogical answer.	Any logical answer (yes, no, partially).
6b	Answer of "yes," or answer of "no" without logical explanation.	"No" with an explanation that making "predictions" with no uncertainty does not facilitate new discoveries.

7	Answer does not logically connect alleles to proteins, and/or does not logically connect proteins to phenotypes.	Answer logically connects alleles with proteins AND connects proteins with phenotypes (e.g., flower color).
8	Answer does not address a concept or skill falling within the realm of the Central Dogma, and/or no study plan is mentioned.	Answer mentions a concept or skill falling within the realm of the Central Dogma AND a study plan.

Full Answer Key



So far, we have used the ClinVar database (ncbi.nlm.nih.gov/clinvar) to check whether a few specific mutations are pathogenic (disease-causing). Now we will harness the power of databases to quickly check LOTS of data!

Do a new ClinVar search in which you type in "BRCA1" only. You should get a lot of matches (>5900) to this search term.

Now look at the column on the left side of the screen (pictured here on the left side of the page). This column allows you to filter the BRCA1 results based on specific criteria. (This is kind of like doing an online search for a product that you want, then restricting the search results so that they only display products that cost less than $10.)

For this exercise, we will look at two of the **Molecular consequence** categories: Frameshift and Missense.

To display only the BRCA1 variations that are Frameshifts (insertions or deletions), click on the word Frameshift in the left-hand column.

(1a) How many BRCA1 frameshift mutations are in this database? *1635*

(1b) Out of all of the Frameshift mutations, how many are definitely pathogenic? (Hint: look at the number next to the word Pathogenic in the left-hand column.) *1466*

(1c) Based on 1a and 1b, what percentage of the Frameshift mutations are definitely pathogenic? *About 90%*

Now go back to the full set of all BRCA1 mutations. (You can do this by clicking Frameshift again to de-select it.) This time, click on Missense (which means the same thing as substitution).

(2a) How many Missense mutations are there in the database? *1710*

(2b) Out of all of the Missense mutations, how many are definitely pathogenic? *79*

(2c) Based on 2a and 2b, what percentage of the Missense mutations are definitely pathogenic? *about 5%*

(3) Based on your answers above, which type of mutation – Frameshift or Missense (Substitution) – is more likely to be pathogenic? *frameshift mutations*

(4) We have studied the frameshift/missense issue with one particular gene (BRCA1). Briefly say how you could use ClinVar to see whether similar patterns hold for the gene BRCA2 (another tumor suppressor involved in breast cancer). (OPTIONAL: Actually do this!)

You could essentially repeat steps 1a through 1c and 2a through 2c with the BRCA2 gene, thus calculating the percentage of BRCA2 frameshift mutations that are pathogenic (1828/1991 => 92%) and the percentage of BRCA2 missense mutations that are pathogenic (47/2940 => 2%).

(5) Does a mutation represent a change in the genetic code? Explain your reasoning.

I would argue that the answer is no. The genetic code is the correspondence between RNA codons (sets of 3 bases) and the amino acids they encode, as shown in the table below. Mutations do not change the table. Instead, they change the DNA base sequence, which changes the RNA base sequence, which changes the amino acid sequence. But the ribosomes are translating the RNA by the same "code" as before.

Second letter

First letter	U	C	A	G	Third letter
U	UUU, UUC Phe UUA, UUG Leu	UCU, UCC, UCA, UCG Ser	UAU, UAC Tyr **UAA Stop** **UAG Stop**	UGU, UGC Cys **UGA Stop** UGG Trp	U C A G
C	CUU, CUC, CUA, CUG Leu	CCU, CCC, CCA, CCG Pro	CAU, CAC His CAA, CAG Gln	CGU, CGC, CGA, CGG Arg	U C A G
A	AUU, AUC, AUA Ile **AUG Met**	ACU, ACC, ACA, ACG Thr	AAU, AAC Asn AAA, AAG Lys	AGU, AGC Ser AGA, AGG Arg	U C A G
G	GUU, GUC, GUA, GUG Val	GCU, GCC, GCA, GCG Ala	GAU, GAC Asp GAA, GAG Glu	GGU, GGC, GGA, GGG Gly	U C A G

Table taken from https://openstax.org/details/biology.

(6a) Earlier, you made predictions about whether substitution/missense and frameshift mutations would lead to disease. To what extent were your predictions correct?

Most of you predicted that frameshift mutations are more likely than substitution mutations to cause disease. This is true as a general pattern, yet there are many exceptions. As you saw in #1-#3 above, not every frameshift mutation is pathogenic, and not every substitution mutation is benign.

(6b) When doing scientific investigations, do you think it is important to make predictions that you know will be right? Explain.

No, for at least two reasons.

- *While it can be satisfying to be right about something, the way science advances is to explore questions whose answers are not already obvious. In trying to answer these hard, unresolved questions, we will sometimes make incorrect predictions, which is a perfectly acceptable part of doing science.*
- *Even predictions that are true on average will not be true in every individual case. We saw examples of this above: frameshift mutations are usually but not always pathogenic, and substitution mutations are usually but not always benign. Weather forecasting is another example; it will not always be right, but that doesn't mean it shouldn't be done.*

(7) Think back to our material on Mendel. Mendel showed, for example, that, depending on which alleles (he called them "factors") a pea plant had, its flowers might be purple or white. Now that you understand transcription and translation, how might a particular allele lead to having purple or white flowers? (Hint: flower color is due to pigments that are synthesized by enzymes, which are proteins.)

Answers will vary; here is one possibility. Imagine a gene that codes for a protein that normally converts a colorless pigment into a purple pigment. Now imagine that there are two alternative alleles for this gene: a "normal" allele that codes for a normal (purple-making) protein, and a "mutant" allele in which a genetic mutation has altered the protein, so that it no longer generates purple. Thus, peas with at least one copy of the "normal" allele have purple flowers, while peas that only have the "mutant" alleles have white flowers.

(8) List one aspect of the Central Dogma on which you would benefit from further practice before the test, and how you will get that practice.

[Answers will vary but should be about the Central Dogma and should include some mention of ***how you will get the needed practice****.]*