Genetic Mutations and Breast Cancer, continued

Name:

Partner's name:

Homeroom:

LO: Predict whether a mutated protein will still work.

SLE: Meet NGSS.

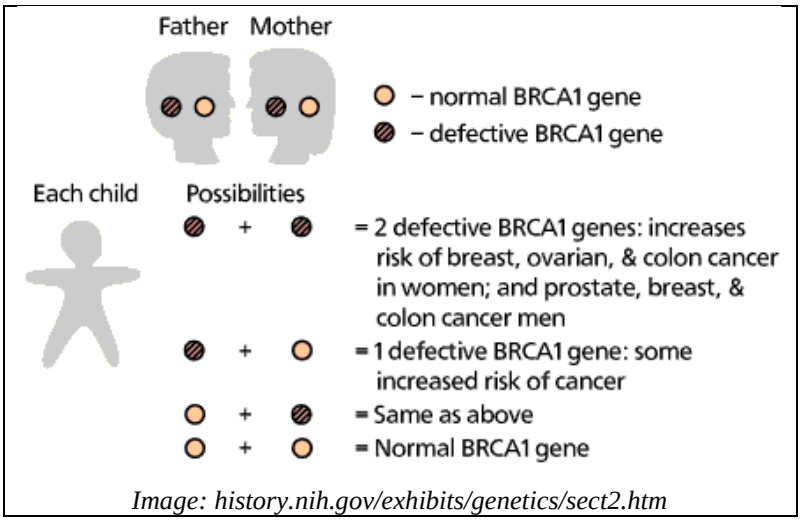

Image: history.nih.gov/exhibits/genetics/sect2.htm

Clinical significance
Conflicting interpretations (316)
Benign (774)
Likely benign (1,055)
Uncertain significance (2,050)
Likely pathogenic (218)
Pathogenic (2,459)
Risk factor (2)

Review status
Practice guideline (0)
Expert panel (2,713)
Multiple submitters (492)
Single submitter (1,506)
At least one star (5,023)
Conflicting interpretations (312)

Allele origin
Germline (5,866)
De novo (0)
Somatic (72)

Method type
Research (637)
Literature only (3,445)
Clinical testing (4,848)

Molecular consequence
Frameshift (1,637)
Missense (1,710)
Nonsense (443)
Splice site (190)
ncRNA (3,801)
Near gene (43)
UTR (203)

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 <u>only</u> 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?

(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.)

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

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?

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

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

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

(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!)

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

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

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

(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.)

(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.