What's a 'variant of uncertain significance?'

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Seven words someone taking a genetic test doesn't want to hear:

"You have a variant of uncertain significance." A VUS.

Instead of a yes or no answer – a gene has a mutation or it doesn't – a VUS is a "not the usual, but we don't know if it's harmful." A maybe.

But like a typo to just one letter on a page, single DNA base substitutions in a gene's sequence might not alter the meaning of the encoded protein.

This can happen as a change:

of one three-base codon to another that specifies the same amino acid
to a similarly-shaped amino acid
in a part of the protein that's not essential to it's function.

Each of us has thousands of variants of uncertain significance, but we don't know about them unless we take a genetic test. A VUS in a member of a family riddled with certain types of cancer can be stressful, especially if a surgical decision rests on genetic test results.

Misinterpretations can have tragic consequences.

Consider the widely-publicized case of Elisha Cooke-Moore, a young woman in Oregon. She's suing a nurse practitioner and surgeon who told her that her genetic test results indicated elevated risk of cancers, which were in her family. Ms. Cooke-Moore, on that advice, had a double mastectomy and hysterectomy, to prevent cancer. It turned out that she had a VUS in the MLH1 gene, which can cause ovarian cancer, although it isn't connected to breast cancer. It's not clear what her providers concluded, but it seems they didn't know what VUS meant. And neither advised their patient to seek the expertise of a genetic counselor.

Sequencing of human genomes has been adding to the gene variant list for years. To ensure that testing labs communicate results in the same language, in 2015 the American College of Medical Genetics and Genomics established guidelines for categorizing gene variants into five risk levels:

- pathogenic
- likely pathogenic
- a variant of uncertain significance (VUS)
- likely benign

- benign

The guidelines state "a variant of uncertain significance should not be used in clinical decision making." And whenever possible, other evidence of disease should be part of a diagnosis. For example, a gene variant deemed "likely pathogenic" might call for additional scans or blood tests to identify specific anomalies. The five categories apply to single-gene diseases like cystic fibrosis and sickle cell disease, but also for cancer risk genes like BRCA1 and BRCA2.

Clinical variant scientists (aka curators) categorize gene variants based on the statistics in research reports and the degree to which the genetic change is predicted to alter the structure and function of the encoded protein. Databases such as the Worldwide Protein Databank and ClinVar.com are important in making determinations.

The label VUS emerges if no reports connect the mystery variant to a phenotype (disease). That's negative and possibly temporary evidence, which can be unnerving. In one case, a young child died of a seizure disorder after being treated with the wrong drug because a gene variant dismissed as a VUS was later found to be pathogenic. If a variant is extremely rare, it might take time to catalog enough cases that associate it with a medical condition.

Delving Into the BRCA Genes

The BRCA proteins are part of molecular machinery that repairs errors in DNA, protecting against mutations that directly cause cancer. The BRCA1 gene is about 126,000 DNA bases and BRCA2 about 85,000, providing a lot of territory for harmless variants to lurk. Thousands are known; about 15% of test-takers get a VUS result.

The three common "Ashkenazi" mutations obliterate the BRCA1 and

BRCA2 proteins because they disrupt the way that the DNA sequence is read in triplets."BRCA1 185delAG" means a neighboring adenine and guanine at position 185 aren't there. "BRCA1 5382insC" means a cytosine is inserted at position 5382. And "BRCA2 6174delT" means a thymine is gone from position 6174.

Adding or removing a number of bases that isn't three or a multiple, like in the most common BRCA mutations, disrupts the reading frame. That introduces an inappropriate "stop" codon mid-gene, resulting in a protein too short to function as it normally would in the mismatch repair response that prevents cancer.

But a mutation that substitutes one DNA base for another, without disrupting the triplet pattern, might not have a drastic, or even noticeable, effect on cancer risk. That's probably the case with Annie, a woman who recently sent me her BRCA1 test results.

Annie's Story

Annie's family has several cases of breast and ovarian cancer on her father's side, and so she was tested 20 years ago, and didn't have any mutations in BRCA1 or BRCA2. But recently, her daughter was tested, and found to have a VUS in BRCA1, but no pathogenic or likely pathogenic mutations. Need Annie or her daughter worry?

The reporting of a VUS reflects the usual checking of journal reports and databases. Here's how some of the logic might work, possible to figure out because BRCA1 is one of the best-studied human genes. A paper, "Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer," lays out the topography of each gene, indicating which parts raise cancer risk.

I delved into Annie's test results.

A DNA base of "G" at position 484 in BRCA1 was, instead, a "C." That changes the encoded amino acid from valine to leucine. But it's probably not harmful for two reasons.

First, leucine is just a little bit larger than valine, with an additional carbon.

Secondly, the switch isn't anywhere near the part of the gene that ups ovarian cancer risk. It's in a "breast cancer cluster region" of DNA bases 179 through 505, but lies outside the hotspot of bases 72-192. The VUS designation means that hardly any variants have turned up that match the one in Annie's daughter, so it can't definitively be called benign or likely benign.

But the VUS issue should resolve with time, as bioinformatics identifies all possible variants of a human gene and establishes sufficient correlations with specific phenotypes, in distinct populations. Gradually, even the two "likelies" may fade, with only benign and pathogenic remaining as genetic testing moves away from the present state of uncertainty.

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