Sequence Variants of Uncertain Significance

What to Do When Genetic Test Results Are Not Definitive

Marc S. Greenblatt, MD

KEYWORDS

• Cancer • Genetic testing • Variants of uncertain significance (VUS) • Gene panels • Pathogenic variant • Hereditary cancer syndrome

KEY POINTS

- Variants of uncertain significance (VUS) comprise a significant and growing number of results from germline testing associated with many hereditary cancer syndromes.
- The biological interpretation and clinical significance of VUS are complex and challenging.
- Unlike pathogenic germline DNA variants, VUS are generally not useful for clinical management; however, the goal of the genetics community is to gather different types of evidence that will eventually lead to the classification of all VUS as either pathogenic or neutral.
- It is important for clinicians, and surgical oncologists in particular, to understand that they can contribute to VUS classification efforts by documenting clinicopathologic data, referring patients and their families to genetic counselors, and encouraging patients to share data and participate in cancer genetics research studies.
- Management of patients at increased cancer risk, and evaluation of difficult genetic variants and their cancer risks, are both complex tasks that rely on combining multiple lines of evidence.

TERMINOLOGY AND DEFINITIONS IN CANCER GENETICS

Clinicians in the coming era will need to be familiar with the basics of genetic terminology and principles, so this article reviews some terms and principles that apply to DNA variations.[1] Some of the nomenclature of DNA variant interpretation is new and confusing to clinicians, and often to researchers as well. Ongoing international efforts

Disclosure: The author has nothing to disclose.
University of Vermont College of Medicine, Given E214, 89 Beaumont Ave, Burlington, VT 05405, USA
E-mail address: marc.greenblatt@uvmhealth.org

Surg Oncol Clin N Am 24 (2015) 833–846
http://dx.doi.org/10.1016/j.soc.2015.06.009 **surgonc.theclinics.com**
1055-3207/15/$ – see front matter

exist to standardize genetic and phenotypic terminology so that the field is more accessible to researchers, clinicians, and patients.[2]

Basic Genetics

Only about 2% of human DNA codes for genes that produce proteins. Much of the remaining 98% of the genome's noncoding DNA is now known to have regulatory functions that are incompletely understood but are the subject of intense study.[3] Current genetic testing for cancer susceptibility generally deals almost exclusively with protein-coding genes. However, it is anticipated that in the future more regulatory regions will be associated with hereditary diseases, including cancer susceptibility syndromes.

A gene is composed of DNA sequences that usually span thousands of base pairs (adenine [A] pairing with thymine [T], guanine [G] pairing with cytosine [C]). The cell reads the DNA code of genes, first producing a complementary strand of messenger RNA (mRNA), by the process of gene transcription. mRNA is then converted into a chain of amino acids that forms a cellular protein by the process of translation using the triplet nucleotide code (3 nucleotide bases translate into 1 amino acid). Genes contain several regions with different functions. In the coding sequences, called exons, the genetic code is read by cellular machinery and converted into a protein. Coding exons are short stretches of DNA separated by sequences called introns, which are stretches of DNA ranging from dozens to thousands of DNA bases that do not code for protein. They are transcribed into mRNA, but are spliced out before mRNA is translated. In addition, there are regulatory sequences that indicate the beginning and end of a gene, and others that code for whether the cell should produce the protein and in what amounts. The consensus normal sequence of a gene and protein is called the wild type. DNA can be altered (mutated) in any gene region,[4,5] and any of these alterations may result in (1) abnormal protein structure, function, and/or expression, causing increased disease susceptibility; or (2) protein structure, function, and expression that is not significantly changed from the normal sequence and does not cause disease.

Clinicians interpret the effects of a DNA change based on knowledge of genetic principles and on observed effects in vivo and in vitro. Reports from clinical genetic testing may indicate abnormalities caused by changes in amino acid, truncation of protein length, abnormal splicing, large gene deletion, and other mechanisms. Interpretation may be uncertain regarding any of these mechanisms. The different types of variants that are seen are:

Missense

Change from one amino acid to another without changing protein length.

Nonsense

Creation of a premature stop codon, coding for a shortened protein that may or may not be transcribed by the cell.

Frameshift

Deletion or insertion of a few DNA nucleotides, not in multiples of 3, that changes the reading frame of the mRNA message. This variant almost always results in a few new incorrect amino acids followed by a premature stop codon.

Insertion or deletion

Insertion or deletions (indels) can be large or small. Small indels are deletions or insertions of a few DNA nucleotides in multiples of 3, which result in the addition or