GUEST EDITORIAL

Garry Cutting

What's in a Name: Mutation versus Variant?

Effective communication between scientists and the public requires the use of words that have well-understood meanings. Similarly, use of a word that means one thing to scientists but something else to the lay public can lead to confusion. This situation can arise when words change in their meaning over time in scientific circles but not among the public, and vice versa. On occasion, dissonance between scientific and societal definitions can cause terms to acquire a stigma. This issue is particularly important when scientific terms are used in medical situations. Certain words may invoke a very different impression for a patient than was intended by a medical professional. For example, the term "mental retardation" is defined scientifically on the basis of the population distribution of IQ, but its use, or rather misuse, by members of the public has led to replacement of the term by "intellectual disability" (Schalock et al., 2007). Thus, effective communication requires careful attention to the meaning of words, particularly when used in different contexts.

One of the most exciting recent developments in biology has been the invention and application of new methods to analyze DNA sequence. The advent of next-generation sequencing has provided a powerful new tool for geneticists and has spawned a new area of technical specialization called "genomics." Sequencing of DNA reveals the locations in our genomes where different nucleotides occur. These alterations can involve anywhere from millions of contiguous nucleotides to a single nucleotide. The ability to resequence the genes and the genomes of humans at ever lower costs has led to the discovery of immense variation among individuals. A minor fraction of this variantion alters the function of a gene such that physical manifestations are produced. When these manifestations affect the health status of an individual, the responsible variant may be labeled a mutation or a disease-causing mutation. The term "mutation" has been used in genetics to imply any permanent change in DNA sequence that is then transmitted to future generations (e.g., http://ghr.nlm.nih.gov/handbook/mutationsanddisorders/genemutation). However, the discovery of many variants in our genomes, most of which are not thought to have a clinical consequence, has caused a rethinking of the use of the term "mutation." This reflection has been driven, in part, by a shift in the public perception of the meaning of the word "mutation."

"Mutation" is defined by most dictionaries as the process that introduces a heritable change into the structure of a gene (King & Stansfield, 2002). The term does not infer a deleterious effect; however, use of "mutation" in association with radiation damage and with disease states has linked a negative connotation to the word (Condit et al., 2002). The problem of inferring deleterious consequences when using the term "mutation" is that some changes in DNA are advantageous from an evolutionary point of view. On the other hand, "variant" is usually defined in terms of an organism that differs in some way from an accepted standard. "Variant" can also be used for phenotypic differences that are not genetic (King & Stansfield, 2002). The application of the term "variant" to changes in DNA structure was popularized by genome-wide association studies of common disorders. "Variant" as opposed to "mutation" is preferred because most of the DNA alterations that contribute risk to complex genetic conditions are of unknown effect and are frequent in the population. These features contrast with DNA changes in Mendelian disorders in which a single change in our genome can cause disease. These changes usually occur within known functional regions of our genomes, are highly penetrant for disease states, and are generally rare, with few alleles exceeding 5% in any population. A well-known example is sickle cell anemia, where the substitution of an adenine for a thymidine in the beta globin gene causes glutamate, the amino acid at position 6, to be replaced by valine. Consequently, "mutation" continues to be used widely in publications reporting the discovery of DNA changes that cause rare disease inherited in a Mendelian fashion (Ng et al., 2010).

The terminology conundrum has been tackled by experts who have preferred the term "variant" so as to avoid the negative connotations that have accrued from the lay perspective. Annotation such as "disease-causing variant" or "pathogenic variant" is recommended when the phenotypic consequence of a variant has been established (Richards et al., 2008). Considering that the goal of scientists and physicians is to annotate variation in our genomes according to disease risk, the use of an unburdened term facilitates understanding in medical and public health settings. This precept is especially important when we consider that some DNA variants cause disease whereas others do not. The proposed approach does not exclude continued use of "mutation," but it does advocate careful consideration of the situation in which the term is used. In summary, the evolving shift in the application of "mutation" or "variant" provides a useful and relevant example of the importance of understanding the meaning of words in science and in society.

Acknowledgment

Adapted from Box 1 in Cutting, G.R. (2014). Annotating DNA variants is the next major goal for human genetics. *American Journal of Human Genetics, 94,* 5–10.

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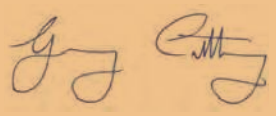

Garry Cutting
gcutting@jhmi.edu

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What's in a Name, & What's in the NGSS?

In the long history of genetics – and of our teaching about it – "mutation" generally has been defined as any change in DNA sequence. In addition, as the other guest editorial in this issue ("What's in a Name: Mutation versus Variant?" by Garry Cutting) points out, the term "mutation" generally has carried a "negative connotation," one that implies a phenotype that is somehow deficient. Next-generation genome sequencing, however, requires that we rethink our approach to the vocabulary we employ in the classroom when we address these concepts.

Massively parallel DNA sequencing has increased tremendously our ability to elaborate biological variation at the level of individual bases. How should we categorize for our students the immense number of changes in DNA sequence, irrespective of species, that have no discernible biological impact or whose effects are yet unexplored? Certainly, as Dr. Cutting points out, not all of these changes will have negative consequences for the individual organisms in which they reside.

References to mutation and variation appear several times in the *Next Generation Science Standards* at the high school level. For example,

- Life science standard 3-2: "Make and defend a claim based on evidence that inheritable genetic *variations* may result from: (1) new genetic combinations through meiosis, (2) viable errors during replication, and/or (3) *mutations* caused by environmental factors."
- Life science standard 4-2: "Construct an explanation based on evidence that the process of evolution primarily results from four factors (including) … The inheritable genetic variation of individuals and species due to *mutation* and sexual reproduction…."

Note the potential in these standards to equate genetic variation with mutation, an unwise conflation in Dr. Cutting's view. We can avoid this confusion by distinguishing process from impact, to wit: the process of mutation is the root source of all genetic variation, whereas the downstream effect of the process – the impact – is highly dependent on a number of interacting variables.

Standard 4-2 provides some assistance with this distinction by placing variation and mutation in an evolutionary context. Using this lens, the instructor can emphasize the variable impact of genetic changes – beneficial, harmful, or neutral – and invite students to suggest the appropriate designation for the change in question.

This newly evident need to differentiate between a variant and a mutation also provides an opportunity to address standards related to the nature of science (e.g., "Scientific Knowledge Is Open to Revision in Light of New Evidence"). Perhaps the most germane high school standard in this category is the following: "Most scientific knowledge is quite durable but is, in principle, subject to change based on new evidence and/or reinterpretation of existing evidence." Nothing in the rapid accretion of sequence data challenges the durability, for example, of the chromosome theory of inheritance or our conception of DNA as the universal information molecule for life on earth. It does, however, require us to rethink the meaning of those data.

Finally, Dr. Cutting's brief essay reminds us that precision in language is critical to the nature and methods of science. We do not enjoy Humpty Dumpty's prerogative (i.e., "When I use a word it means just what I choose it to mean – neither more nor less"). The precision of our language reflects the quality of our thinking, and the words we choose to describe natural phenomena must make sense to our colleagues if they are to become part of our common vocabulary and prove useful in scientific inquiry.

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Joseph D. McInerney
Executive Vice President,
American Society of Human Genetics
NABT president, 1990

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