© American College of Medical Genetics and Genomics

An openly available online tool for implementing the ACMG/AMP standards and guidelines for the interpretation of sequence variants

To the Editor: The joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) on standards and guidelines for the interpretation of sequence variants, published in the May 2015 issue of *Genetics in Medicine*, is an excellent resource and reference for interpreting the clinical significance of next-generation sequencing variants using multiple categories and degrees of evidence.[1] In our activities concerned with variant interpretation, we use the directives in the article extensively.

To facilitate the process, we created an interactive tool based on the article that has been a valuable addition to our process, and we believe it would be useful for others performing variant interpretation.

We have been using the standards and guidelines to classify variants identified using a next-generation sequencing gene panel for individuals with suspected forms of monogenic diabetes, such as maturity-onset diabetes of the young, as part of the Personalized Diabetes Medicine Program, a member project in the National Human Genome Research Institute–funded IGNITE (Implementing Genomics in Practice) Network. This program uses patient characteristics and family history to identify individuals likely to have a monogenic etiology for their diabetes mellitus, which is challenging owing to the similarity of clinical presentation between monogenic diabetes and more common forms of diabetes. Accurate interpretation of variant pathogenicity is crucial for correctly diagnosing monogenic diabetes. The criteria set forth by the article have been tremendously valuable for classifying whether identified variants are causative for the diabetic phenotype or simply coincidental with a more complex or other unidentified etiology. In light of recent reports calling into question the pathogenicity of some purported monogenic diabetes variants, assigning accurate variant classifications is paramount for our study.[2]

The openly available online tool we have developed efficiently classifies variants based on the evidence categories outlined in the article. This site displays the evidence categories and descriptions from Tables 3 and 4 with simple checkboxes for selecting appropriate criteria. The site then incorporates the algorithm in Table 5 to automatically assign the pathogenicity or benign impact based on the selected evidence categories. Because our process often requires analyzing multiple variants per patient, we have also allowed the option of aggregating each variant into an exportable table at the foot of the website for easy documentation of the variant review process for our records. The tool is available at http://medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html.

In our experience, we found that it can be challenging to evaluate each category of criteria, total the number of criteria based on evidence of pathogenicity or benign impact, and then manually classify sequence variants based on the rules of the article, especially for multiple variants per sample. The online tool we have developed allows us to focus on identifying and evaluating each piece of evidence without having to manually tabulate and interpret the results. We are grateful to the authors of the article, including the entire ACMG Laboratory Quality Assurance Committee, for developing and designing such a rigorous and well-designed system for variant interpretation that could be translated into an automated online tool.

DISCLOSURE

The authors declare no conflict of interest.

Jeffrey Kleinberger, BSc[1], Kristin A. Maloney, MS, MGC[1], Toni I. Pollin, MS, PhD[1] and Linda Jo Bone Jeng, MD, PhD[1]

[1]Program for Personalized and Genomic Medicine, Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA. Correspondence: Linda Jo Bone Jeng (ljeng@som.umaryland.edu)

REFERENCES

1. Richards S, Aziz N, Bale S, et al.; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–424.
2. Flannick J, Beer NL, Bick AG, et al. Assessing the phenotypic effects in the general population of rare variants in genes for a dominant Mendelian form of diabetes. *Nat Genet* 2013;45:1380–1385.

Advance online publication 17 March 2016. doi:10.1038/gim.2016.13