COMMENT

An all-encompassing variant classification system proposed

Philippe M. Campeau[1] ✉

European Journal of Human Genetics (2022) 30:139; https://doi.org/10.1038/s41431-021-00992-w

In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP) published guidelines establishing a classification system for sequence variant interpretation [1]. These guidelines were quickly adopted, as they allowed the uniformization of variant annotation in clinical reports and research studies [2]. They were designed to be broadly applicable to thousands of disease genes and clinical scenarios, and they have affected how most clinical genetics professionals present variant information to families. However, the classification presents shortcomings, for example in classifying variants of moderate to low penetrance, classifying recessive variants, or variants in genes contemporaneously associated with diseases. It was also not designed to classify copy number variants (CNVs). The Variant of Unknown Significance (VUS) category is broad and captures many ultra-rare variants, for example when there are too few elements to suggest pathogenicity or when there are conflicting pathogenicity clues. When reports are read by non-experts, the subtleties as to why a variant is classified as a VUS are often not well understood, and the result can be interpreted to be normal, or to confirm a diagnosis, when it may not be the case. The guidelines do allow for laboratories to add extra tiers or subcategories to the classification, and these are especially useful when variants are classified as VUSs. However, these additional subcategories are generally not accepted when submitting data to ClinVar.

Several modifications or additions to the classification system have been proposed, such as the Sherloc classification scheme from the company Invitae [3], or efforts of the NIH-funded Clinical Genome Resource (ClinGen) such as the CNV Interpretation Calculator, a Bayesian calculation framework, and gene- or gene group-specific Variant Curation Expert Panels [4–6]. In 2019, an ad hoc working group of the European Society of Human Genetics (ESHG) proposed a two-dimensional system for variant classification. The goal of such a system was to address some of the limitations of the ACMG-AMP classification system for certain variant types or genes, and to be more broadly applicable without requiring gene-specific classification systems, for example. This effort has evolved into the stepwise ABC classification system, which takes into consideration functional and clinical available data, and allows for an optional comment to reflect, for example, local policy [7]. This classification can be used as an alternative to the ACMG-AMP classification or an addition to it (i.e. as an optional tier), and is not ESHG Board-endorsed. Its use by a broad array of laboratories, and the description of the ABC classification and grades in the comments section of ClinVar submissions, for example, could allow for a wide assessment of its clinical utility, which is already clear to many.

REFERENCES

1. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. 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: Off J Am Coll Med Genet. 2015;17:405–24.
2. Niehaus A, Azzariti DR, Harrison SM, DiStefano MT, Hemphill SE, Senol-Cosar O, et al. A survey assessing adoption of the ACMG-AMP guidelines for interpreting sequence variants and identification of areas for continued improvement. Genet Med: Off J Am Coll Med Genet. 2019;21:1699–701.
3. Nykamp K, Anderson M, Powers M, Garcia J, Herrera B, Ho YY, et al. Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. Genet Med: Off J Am Coll Med Genet. 2017;19:1105–17.
4. Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med: Off J Am Coll Med Genet. 2020;22:245–57.
5. Tavtigian SV, Greenblatt MS, Harrison SM, Nussbaum RL, Prabhu SA, Boucher KM, et al. Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework. Genet Med: Off J Am Coll Med Genet. 2018;20:1054–60.
6. Harrison SM, Biesecker LG, Rehm HL. Overview of specifications to the ACMG/AMP variant interpretation guidelines. Curr Protoc Hum Genet. 2019;103:e93.
7. Houge G, Laner A, Cirak S, de Leeuw N, Scheffer H, den Dunnen JT: et al. system for classification of any type of genetic variant. Eur J Hum Genet. 2021.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Philippe M. Campeau.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

[1]Department of Pediatrics, University of Montreal and CHU Sainte-Justine, Montreal, QC, Canada. ✉email: p.campeau@umontreal.ca

Received: 12 October 2021 Accepted: 17 October 2021
Published online: 29 October 2021