Title: Lack of specificity of ACMG classification rules decreases inter-curator concordance. ClinGen's adaptation of ACMG's framework to standardize interpretation of MYH7 related cardiomyopathy variants.

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Abstract:

Background: Recognition that variants in Mendelian disease genes are often classified differently in different labs has signaled the need for advances in variant classification systems. Recently, ACMG published updated guidelines, intended to serve as a framework for classifying Mendelian variants across all areas of genetics. We investigated the application of these new guidelines to *MYH7* and cardiomyopathy.

Methods: Ten *MYH7* variants were independently reviewed by three members of the ClinGen Cardiovascular Working Group. Reviewers classified the variants using both the new ACMG criteria and criteria previously developed by each reviewer's cardiomyopathy genetics team. This analysis provided the foundation for an in-depth review of the ACMG criteria and the development of adapted rules with optimized specificity for *MYH7*.

Results: Classification concordance was 8/10 for institutional criteria and 3/10 for ACMG guidelines. Disagreement between institutional classifications arose mainly from privately held data, while disagreement between ACMG classifications was largely due to ACMG criteria being applied differently by reviewers. Six of seven established pathogenic and likely pathogenic variants were classified as variants of uncertain significance with the ACMG criteria by at least one of the three reviewers. Subsequent in-depth review of the ACMG criteria resulted in 18 rule adaptations that are critical to provide optimal specificity for *MYH7*. Nine rules were modified, including changes informed by cardiomyopathy specific characteristics such as incomplete penetrance, prevalence of disease-causing alleles in the general population, and the existence of 1-5% of patients with >1 pathogenic variant. Eight rules were deemed inapplicable to *MYH7*, including loss of function as a known

mechanism of disease and mutational hotspots. One rule was added to enable using the number of unrelated cases as a criterion supporting pathogenicity. Fifteen rule revisions were broadly applicable across cardiovascular genetics, reflecting a general lack of specificity.
Conclusions: The use of ACMG guidelines in their current form can decrease the concordance of variant classifications. Expert review is therefore critical to adapt this new framework to disease domains and to reflect disease and gene specific characteristics and to enable consistent application. Our work serves as a stepping stone for additional genes and diseases.