THE USE OF GENE-SPECIFIC CLASSIFICATION GUIDELINES VS ACMG 2015: MODY CASE STUDY

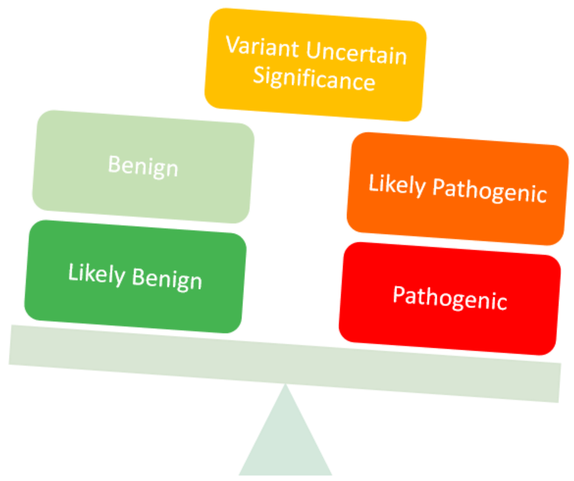
Paulo Dario[1,2]*, Margarida Vaz[1]*, Gisela Gaspar[1], Mafalda Bourbon[1,2]

[1]Department of Health Promotion and Prevention of Noncommunicable Diseases, National Institute of Health Doutor Ricardo Jorge, 1649-016 Lisbon, Portugal; [2]BioISI - BioSystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisbon, 1749-016 Lisbon, Portugal.

* These authors were equal contributors to this study.

Introduction

Maturity-Onset Diabetes of the Young (MODY) is a form of diabetes characterized as a dominant monogenic disorder. It is caused by pathogenic or likely pathogenic variants in any of the 14 genes currently associated with the disease. Since 2015, our laboratory has employed the classification algorithm guidelines established by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) for variant classification. However, the process of variant classification under these guidelines can be intricate and time-intensive. Additionally, the data required for assessing pathogenicity are often challenging to interpret and may be too generalized for application to specific diseases like MODY. A significant issue arising from reliance on these guidelines is the frequent categorization of variants as Variants of Uncertain Significance (VUS). These variants neither clearly explain the disease's cause nor can they be definitively classified as benign. **To address these limitations, the Monogenic Diabetes Variant Classification Expert Panel (MDEP VCEP) has developed specialized guidelines for classifying MODY variants, particularly those found in the GCK, HNF1A, and HNF4A genes. These tailored guidelines aim to enhance the precision and relevance of variant classification in the context of MODY.**



Our objective is to determine whether variants initially classified as VUS under the 2015 ACMG guidelines can achieve a definitive classification when re-evaluated using the specific criteria set forth by the MDEP guidelines.

Methods

In this study, we conducted a comparative analysis of two variants identified in patients from the Portuguese MODY Study. These variants were initially classified as Variants of Uncertain Significance (VUS) under the 2015 ACMG guidelines. Subsequently, they were reclassified using the MDEP guidelines. Additionally, their classifications were confirmed through ClinVar.

Results

HNF1A c.599G>A, (p.Arg200Gln)

ACMG original guidelines	MDEP-VCEP Specifications to ACMG guidelines
• Criteria Met: • PM2 • PP3 • PP4	• Criteria Met: • PS4 (information shared by MDEP curators) • PP1_strong (information shared by MDEP curators) • PS3_suporting • PM2_suporting • PP3 • PP4_moderate
↓ VUS	↓ Pathogenic FDA A. Db

GCK: c.1268T>A, p.(Phe423Tyr)

ACMG original guidelines	MDEP-VCEP Specifications to ACMG guidelines
• Criteria Met: • PM2 • PP3 • PP4	• Criteria Met: • PP2 • PM2_suporting • PP3 • PP4
↓ VUS	↓ VUS

Discussion

- **The 2015 ACMG-AMP guidelines were a crucial initial step in standardizing procedures for variant classification and interpretation. This approach significantly advanced the uniformity of variant reporting, aiming to provide clinicians with a more transparent understanding of genetic test results. However, these guidelines were somewhat broad, covering a wide spectrum of Mendelian disorders without sufficient specificity for certain conditions, such as MODY diabetes. This generality led to variability in classification practices across different laboratories, especially for criteria with ambiguous definitions, such as patient phenotype, mutational hotspots, and mechanisms of disease for missense variants.**
- **In response to these challenges, the MDEP-VCEP developed tailored guidelines for three specific genes associated with MODY diabetes: GCK, HNF1A, and HNF4A. These guidelines offer detailed interpretations of criteria, including problematic protein regions, specific fasting glucose and HbA1C levels, and a decision tree for large deletions, which was not included in the original guidelines. They also allow for the adjustment of criteria strength based on the available evidence, adding a layer of flexibility. The adapted guidelines performed by the ClinGen expert groups and the work performed by ClinGen groups is FDA approved.**
- **Since 2018, the Department of Health Promotion and Noncommunicable Diseases at the Instituto Nacional de Saúde Dr. Ricardo Jorge has been conducting an ongoing study on Monogenic Diabetes, involving 174 participants. During this study, variants frequently categorized as VUS were identified, including HNF1A c.599G>A/(p.Arg200Gln) and GCK: c.1268T>A/p.(Phe423Tyr). The HNF1A variant was reclassified as Pathogenic, a decision influenced not only by the updated guidelines but also by collaborative data sharing between institutions. This robust evidence included the number of affected individuals and their phenotypes, what lead to the upgrade of the variant classification. While the classification of the GCK variant remained VUS, it has not yet been curated by the MDEP group, so it is possible that a future re-evaluation with additional evidence can lead to a definitive classification.**

In conclusion, the implementation of disease-specific guidelines has improved the precision of variant classification, as evidenced by the reclassification of at least one variant in our MODY Diabetes Study. The MDEP group continues to review and update variant classifications submitted to ClinVar, sharing their findings. As Next-Generation Sequencing becomes more commonplace, we anticipate encountering an increasing number of rare variants with limited background information. To address this, laboratories should adhere to consistent guidelines for variant classification and regularly consult ClinVar for updates on variant classifications and most important clinicians and labs should share clinical information, crucial for variant classification.

References

Information about MODY Diabetes Study

mafalda.bourbon@insa.min-saude.pt gisela.gaspar@insa.min-saude.pt paulo.dario@insa.min-saude.pt margarida.vaz@insa.min-saude.pt