Optimization of the ACMG-AMP Criteria for CDH1 Variant Classification

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Introduction

CDH1 mutations cause Hereditary Diffuse Gastric & Lobular Breast Cancer (HDGC – OMIM 137215). Heterozygotes for a germline CDH1 truncating pathogenic variant present an estimated cumulative risk of developing gastric cancer 70% (95% CI, 59%-80%) for males and 56% (95% CI, 44%-69%) for females. Women also have a 42% (95% CI, 23%-68%) risk of developing lobular breast cancer. CDH1 is a clinically actionable gene. Current recommendations include, for women, consideration of breast MRI starting at 30 years of age and risk-reducing mastectomy. Prophylactic gastrectomy is recommended for both genders between the age of 20 and 30 (annual upper endoscopy following the dedicated Cambridge protocol with a minimum of 30 biopsies for people who do not undergo gastrectomy). Therefore, it is imperative to detect and correctly classify variants in CDH1 according to their pathogenicity. With this in mind, the ClinGen Hereditary Cancer Working Group selected CDH1, together with PTEN and TP53, as high priorities genes and created a CDH1 working group (WG).

The CDH1 WG is an expert panel assembled from CDH1 experts encompassing clinicians, scientists and clinical laboratory diagnosticians, with a primary goal to optimize the 2015 ACMG/AMP Variant Interpretation Guidelines specific to CDH1.

Here we present the CDH1 WG rule specifications to the ACMG/AMP criteria, which after systematic evaluation with a series of test variants will be finalized and incorporated into the group's curation process, as part of the CDH1 ClinGen Expert Panel application. The group recommendations for pathogenic and benign criteria optimizations for CDH1 include: standalone and strong benign CDH1 specific allele frequency cutoffs; gene specifications for splicing; recommendations for the use of computational and functional evidence; standardization of acceptable HDGC diagnostic criteria and minimal clinical information. These criteria will be validated by comparing clinical, population, computational, and functional data, among multiple institutions participating in the CDH1 WG.

Evaluation of CDH1-Specific Criteria

Working groups were assembled to analyze and present current knowledge related to CDH1 surrounding each ACMG/AMP criteria evidence type. The group agreed to the following process for drafting, testing, and adopting criteria.

- Identify ACMG/AMP criteria that need optimization
- Evidence-based analysis of suggested optimizations
- Experts/ClinGen feedback: Make edits/adjustments as needed
- Experts vote for proposed optimizations
- Application to ClinGen for formal Expert Panel status

Proposed Optimizations (in red)

This table outlines the proposed optimizations to the ACMG/AMP criteria for CDH1. The updates include the removal of specific allele frequency cutoffs, the inclusion of computational and functional data, and the standardization of HDGC diagnostic criteria.

Functional Data

This section highlights the importance of functional data in assessing variant impact, including in vitro and in vivo studies, and computational predictions.

Other (Clinical Data)

This section includes criteria for clinical data, such as family history and clinical behavior, which are crucial for a comprehensive evaluation of variant pathogenicity.

Testing CDH1 Optimizations

Most proposed optimizations by the CDH1 WG focus on the assessment of CDH1 missense alterations. With this in mind, we selected 17 missense alterations with extensive literature in order to compare functional assays and in silico analysis to clinical data. Color code: Red/yellow= pathogenic criteria met fully/partially; Green/light green=benign criteria met fully/partially. DGC=Diffuse Gastric Cancer ILC=Invasive Lobular Breast Cancer.

Future Directions

Following expert votes and final edits to the criteria and curation process, an application will be submitted to ClinGen for formal Expert Panel status.

References