Recommendations by the ClinGen Rett/Angelman-like Expert Panel for Gene-specific Variant Interpretation Methods

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Abstract

The genes MECP2, CDKL5, FOXP1, UBE3A, SLC9A6, and TCF4 present unique challenges for current ACMG/AMP variant interpretation guidelines. To address those challenges, the Rett and Angelman-like Disorders Variant Curation Expert Panel (Rett/AS VCEP) drafted gene-specific modifications. A pilot study was conducted to test the clarity and accuracy of using the customized variant interpretation criteria. Multiple curators obtained the same interpretation for 78 out of the 87 variants (~90%), indicating appropriate usage of the modified guidelines the majority of times by all the curators. The classification of 13 variants changed using these criteria specifications compared to when the variants were originally curated and as present in ClinVar. Many of these changes were due to internal data shared from laboratory members however some changes were because of changes in strength of criteria. There were no two step classification changes and only 1 clinically relevant change (Likely pathogenic to VUS). The Rett/AS VCEP hopes that these gene-specific variant curation rules and the assertions provided help clinicians, clinical laboratories, and others interpret variants in these genes but also other fully penetrant, early-onset genes associated with rare disorders.

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RettAngelman_for Hum Mut_V3.doc available at <https://authorea.com/users/428860/articles/>

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Tables 1, 3, 4_ Rett_Angelman genes.doc available at <https://authorea.com/users/428860/articles/532666-recommendations-by-the-clingen-rett-angelman-like-expert-panel-for-gene-specific-variant-interpretation-methods>

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Table 2_ ACMG_Specifications_Rett_AS_v11.doc available at <https://authorea.com/users/428860/articles/532666-recommendations-by-the-clingen-rett-angelman-like-expert-panel-for-gene-specific-variant-interpretation-methods>