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Multiple Endocrine Neoplasia Type 2 (MEN2) and RET Specific Modifications of the ACMG/AMP Variant Classification Guidelines and Impact on the MEN2 RET Database

Rebecca L. Margraf[1], Rachel Z. Alexander[2], Makenzie L. Fulmer[1], Christine Miller[1], Elena Coupal[1], and Rong Mao[1]

[1]ARUP Institute for Clinical and Experimental Pathology
[2]OhioHealth

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Abstract

The Multiple Endocrine Neoplasia type 2 (MEN2) *RET* proto-oncogene database, originally published in 2008, is a comprehensive repository of all publicly available *RET* gene variations associated with MEN2 syndromes. The variant-specific genotype/phenotype information, age of earliest reported medullary thyroid carcinoma onset, and relevant references with a brief summary of findings are cataloged. The ACMG/AMP 2015 consensus statement on variant classification was modified specifically for MEN2 syndromes and *RET* variants using ClinGen sequence variant interpretation working group recommendations and ClinGen expert panel manuscripts, as well as manuscripts from the American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma and other MEN2 *RET* literature. The classifications for the 166 single unique variants in the MEN2 *RET* database were reanalyzed using the MEN2 *RET* specifically modified ACMG/AMP classification guidelines. Applying these guidelines added two new variant classifications to the database (likely benign and likely pathogenic) and resulted in clinically significant classification changes (*e.g.* from pathogenic to uncertain) in 16.9% (28/166) of the original variants. Of those clinically significant changes, the highest percentage of changes, 46.4% (13/28), were changes from uncertain to benign or likely benign. The modified ACMG/AMP criteria with MEN2 *RET* specifications will optimize and standardize *RET* variant classifications.

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