Impact of genetic reclassification on ARVC diagnosis based on the 2010 task force criteria

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Introduction: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited condition, which is associated with potentially life-threatening ventricular arrhythmias in the young. Approximately 60% of patients carry a possibly disease-causing genetic variant.

Purpose: The aim of this study was to investigate the impact of the 2015 American College of Medical Genetics (ACMG) Criteria on ARVC diagnosis based on the 2010 Modified Task Force Criteria (TFC).

Methods: The study included 79 patients from the Swiss ARVC Registry who harbored a genetic variant deemed to be associated with the disease at initial screening, and classified them as definite, borderline or possible ARVC. Every variant found was re-classified on Varsome Genetics, based on the 2015 ACMG Criteria. Clinical information was then assessed at last available follow-up of every patient and ARVC diagnosis was reclassified based on the newest genetic evidence available.

Results: In 42 out of 79 patients (53.2%), genetic variants were reclassified. Out of these, 33 variants (41.8%) were downgraded from pathogenic (P) / likely pathogenic (LP) to either variants of unknown significance (VUS) or benign (B) / likely benign (LB). Three patients (3.8%) were upgraded from VUS / LP to P. Out of the 12 variants initially classified as VUS, 9 (75%) were reclassified as B or LB. Overall, 13 patients (16.5%) were downgraded from their initial diagnosis (11 from definite to borderline and 2 from borderline to possible).

Conclusion: A significant proportion of patients with ARVC diagnosed based on the 2010 TFC were reclassified when the 2015 ACMG Criteria were taken into consideration. These findings may have clinical consequences, particularly for genetic cascade screening of family members of ARVC patients and necessitate reassessment of genetic variants of index patients who were previously diagnosed with ARVC.

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