Title: Arrhythmogenic Right Ventricular Cardiomyopathy *GeneReview* — Less Common Genetic Causes
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Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

CTNNA3

Gene structure. According to the NCBI Reference sequence *CTNNA3* contains 18 exons with an mRNA 2687 bp in length.

Pathogenic variants. van Hengel et al reported two probands with missense variants c.281T>A (p.Val94Asp) and c.2293_2295delTTG (p.del765Leu). Functional studies supported a role for these changes in abnormal function of the protein [van Hengel et al 2013].

Table 5. Selected Pathogenic *CTNNA3* Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.281T>A	p.Val94Asp	NM_013266.3 NP_037398.2
c.2293_2295delTTG	p.Leu766del	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The CTNNA3 NP_037398.2 transcript encodes a 895 amino acid protein belonging to the vinculin/alpha catenin family, alphaT-catenin. The protein plays a role in cell-cell adhesion in muscle cells. The alphaT-catenin protein directly couples the adherens junction to the actin cytoskeleton within the intercalcated discs [Wickline et al 2016].

Abnormal gene product. The p.Val94Asp pathogenic variant has been shown to alter alphaT-catenin dimerization potential to disrupt beta-catenin binding and cellular localization [Wickline et al 2016].

RYR2

Gene structure. The transcript variant NM_001035.2 comprises 105 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Multiple pathogenic variants have been identified in *RYR2* that confer a phenotype more consistent with ARVC and phenotypically different from CPVT [Roux-Buisson et al 2014]. These variants differ from those found in *RYR2* in CPVT (see Table 2).

Normal gene product. *RYR2* encodes a 4967-amino acid protein (NP_001026.2) that is a 565-kd monomer. The ryanodine receptor 2 regulates calcium flux in the

intracellular space and mediates cardiac muscle excitation-contraction coupling [Tiso et al 2001, Roux-Buisson et al 2014].

Abnormal gene product. Pathogenic variants in *RYR2* are thought to result in an uncontrolled calcium leak in the cardiac myocyte, leading to arrhythmia.

TGFB3

Gene structure. The gene comprises seven exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Two pathogenic variants have been described, one in the 5' untranslated region of the gene and the second in the 3' untranslated region of the gene [Beffagna et al 2005].

Normal gene product. *TGFB3* encodes for transforming growth factor beta-3, which encodes for a cytokine-stimulating fibrosis and modulates cell adhesion.

Abnormal gene product. It is currently unknown how pathogenic variants in *TGFB3* cause ARVC.

References

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