Title: Arrhythmogenic Right Ventricular Cardiomyopathy GeneReview — Less Common Genetic Causes
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Updated: May 2017
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**

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.281T&gt;A</td>
<td>p.Val94Asp</td>
<td>NM_013266.3</td>
</tr>
<tr>
<td>c.2293_2295delTTG</td>
<td>p.Leu766del</td>
<td>NP_037398.2</td>
</tr>
</tbody>
</table>

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 intercalated 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

**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**


