

Variant: *NM_001204.7(BMPR2):c.529+2T>C*

Version: 1.0

CA350338507 [↗](#)

425800 (ClinVar) [↗](#)

Gene: BMPR2 ([HGNC:659](#))

Condition: pulmonary arterial hypertension ([MONDO:0015924](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 26778d12-b52a-42a4-9b61-c6e1048a2505

Approved on: 2024/5/3

Published on: 2024/5/3

HGVS expressions

NM_001204.7:c.529+2T>C

NM_001204.7(BMPR2):c.529+2T>C

NC_000002.12:g.202513831T>C

CM000664.2:g.202513831T>C

NC_000002.11:g.203378554T>C

CM000664.1:g.203378554T>C

NC_000002.10:g.203086799T>C

NG_009363.1:g.142505T>C

ENST00000374580.10:c.529+2T>C

ENST00000638587.1:c.460+2T>C

ENST00000374574.2:c.529+2T>C

ENST00000374580.8:c.529+2T>C

NM_001204.6:c.529+2T>C

Uncertain Significance

Met criteria codes **2**

PM2_Supporting

PVS1_Strong

Not Met criteria codes **2**

PP3

PM4

Evidence Links **0**

Expert Panel

Pulmonary Hypertension VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Pulmonary Hypertension

Expert Panel Specifications to the ACMG/AMP Variant

Interpretation Guidelines for BMPR2 Version 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Pulmonary Hypertension VCEP

The NM_001204.7(BMPR2) c.529+2T>C variant is located in the canonical donor splice site of intron 4. It is predicted to cause skipping of biologically relevant exon 4 (111 bp), resulting in an in-frame deletion of amino acids Ser140-Thr176 within the transmembrane domain, that is predicted to escape nonsense-mediated decay (PVS1_strong). The predictions were recorded under PVS1, so PP3 was not applied to avoid double counting. Although the variant is predicted to cause a change in the length of the protein due to in-frame deletion, no functional data are available and thus PM4 was not applied. This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_supporting). In

summary, this variant meets the criteria to be classified as uncertain significance for autosomal dominant pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: PVS1_strong, PM2_supporting. (VCEP specifications version 1.1, 1/18/2024)

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD controls (v2.1.1 and v3.1.2)
PVS1_Strong			The variant (NM_001204.7 (BMPR2): c.529+2T>C) occurs within the canonical splice donor site (+2) of intron 4. Splice AI predicts loss of donor splice site (score 0.97) that may lead to skipping of biologically relevant exon 4 (111bp), resulting in an in-frame deletion of 37 amino acids (140-176) present in the transmembrane domain. No experimental data are available for this variant.

Not Met criteria codes

PP3			The computational splicing predictor Splice AI gives a score of (0.97) for donor splice site loss, predicting that the variant disrupts the donor splice site of intron 4 of BMPR2. However, the predictions were recorded under PVS1 so PP3 was not applied to avoid double counting.
PM4			The variant (NM_001204.7: c.529+2T>C) is predicted to cause a change in the length of the protein due to in-frame deletion of 37 amino acids (140-176). However, no functional data are available to support this prediction, which has been scored under PVS1.

Curation History



 

 

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