Variant: NM_001754.5(RUNX1):c.281G>C (p.Ser94Thr)

Version: 1.0

CA410203693

3068220 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2e03431d-79bf-461e-ba49-709ca7880255
Approved on: 2025-01-15
Published on: 2025-01-15

HGVS expressions

NM_001754.5:c.281G>C
NM_001754.5(RUNX1):c.281G>C (p.Ser94Thr)
NC_000021.9:g.34886913C>G
CM000683.2:g.34886913C>G
NC_000021.8:g.36259210C>G
CM000683.1:g.36259210C>G
NC_000021.7:g.35181080C>G
NG_011402.2:g.1102799G>C
ENST00000675419.1:c.281G>C
ENST00000300305.7:c.281G>C
ENST00000344691.8:c.200G>C
ENST00000358356.9:c.200G>C
ENST00000399237.6:c.245G>C
ENST00000399240.5:c.200G>C
ENST00000437180.5:c.281G>C
ENST00000455571.5:c.242G>C
ENST00000482318.5:c.59-6200G>C
NM_001001890.2:c.200G>C
NM_001122607.1:c.200G>C
NM_001754.4:c.281G>C
NM_001001890.3:c.200G>C
NM_001122607.2:c.200G>C

Uncertain Significance

Met criteria codes 3

PP3 PM1_Supporting PM2_Supporting

Not Met criteria codes 23

PS1 PS2 PS3 PS4 BA1 PP1 PP2 PP4 PM3 PM5 PM4 PM6 PVS1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2

Evidence Links 0

Expert Panel

Myeloid Malignancy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Myeloid Malignancy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.5(RUNX1):c.281G>C (p.Ser94Thr) is a missense variant with a REVEL score ≥ 0.88 (0.931) (PP3). This variant is located within the Runt Homology Domain (AA 89-204), but does not occur in an established hotspot residue (PM1_supporting). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting). This variant has been reported as likely pathogenic by clinical testing by the Center for Genomic Medicine, King Faisal Specialist Hospital and Research Center (ClinVar ID 3068220), however, PS1 was not applied because it was not curated using the MM-VCEP rules for RUNX1. In summary, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PP3, PM1_supporting, PM2_Supporting.

Met criteria codes

PP3	ℹ	✓	This missense variant has a REVEL score ≥ 0.88 (0.931) (PP3).
PM1_Supporting	ℹ	✓	This variant affects one of the other residues (AA 89-204) within the RHD, specifically residue 94 (PM1_Supporting).
PM2_Supporting	ℹ	✓	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).

Not Met criteria codes

PS1	ℹ	✗	This variant c.281G>C (p.Ser94Thr) has been reported as likely pathogenic by clinical testing by the Center for Genomic Medicine, King Faisal Specialist Hospital and Research Center (ClinVar ID 3068220), however, PS1 was not applied because it was not curated using the MM-VCEP rules for RUNX1.
PS2		✗	De novo data for this variant has not been reported in literature.
PS3	ℹ	✗	In vitro or in vivo functional data has not been reported for this variant in the literature.
PS4	ℹ	✗	The prevalence of the variant in affected individuals has not been reported to be significantly increased compared with the prevalence in controls.
BA1	ℹ	✗	This variant does not have a MAF ≥ 0.0015 (0.15%) in any general continental population dataset.
PP1	ℹ	✗	Segregation data for this variant has not been reported in literature.
PP2		✗	This rule is not applicable for MM-VCEP
PP4		✗	This rule is not applicable for MM-VCEP

PM3		✖	This rule is not applicable for MM-VCEP
PM5	ℹ	✖	There has not yet been a different missense change determined to be pathogenic at this amino acid residue.
PM4	ℹ	✖	This variant is not an in-frame deletion/insertion.
PM6	ℹ	✖	De novo data for this variant has not been reported in literature.
PVS1	ℹ	✖	This variant is not a null variant.
BS1	ℹ	✖	This variant does not have a MAF between 0.00015 (0.015%) and 0.0015 (0.15%) in any general continental dataset.
BS4	ℹ	✖	Segregation data for this variant has not been reported in literature.
BS3	ℹ	✖	In vitro or in vivo functional data has not been reported for this variant in the literature.
BS2		✖	This rule is not applicable for MM-VCEP
BP5		✖	This rule is not applicable for MM-VCEP
BP7	ℹ	✖	This variant is not a synonymous or intronic variant.
BP4	ℹ	✖	This missense variant does not have a REVEL score < 0.50.
BP3		✖	This rule is not applicable for MM-VCEP
BP1		✖	This rule is not applicable for MM-VCEP
BP2	ℹ	✖	This variant has not been observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.

Curation History

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