

Variant: NM_001754.5(RUNX1):c.991A>C (p.Ser331Arg)

Version: 1.0

CA410148750 [↗](#)

1023243 (ClinVar) [↗](#)

Gene: RUNX1 ([HGNC:861](#))

Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome ([MONDO:0011071](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 246d841c-9c31-4705-9ec3-f81fb633152d

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HGVS expressions

NM_001754.5(RUNX1):c.991A>C (p.Ser331Arg)

NM_001754.5:c.991A>C

NC_000021.9:g.34792587T>G

CM000683.2:g.34792587T>G

NC_000021.8:g.36164884T>G

CM000683.1:g.36164884T>G

NC_000021.7:g.35086754T>G

NG_011402.2:g.1197125A>C

ENST00000675419.1:c.991A>C

ENST00000300305.7:c.991A>C

ENST00000344691.8:c.910A>C

ENST00000399240.5:c.718A>C

ENST00000437180.5:c.991A>C

ENST00000482318.5:c.*581A>C

NM_001001890.2:c.910A>C

NM_001754.4:c.991A>C

NM_001001890.3:c.910A>C

Uncertain Significance

Met criteria codes **2**

PM2_Supporting

BP4

Not Met criteria codes **24**

PS1

PS2

PS3

PS4

BA1

PP1

PP2

PP3

PP4

PM1

PM3

PM5

PM4

PM6

BS2

BS1

BS4

BS3

BP3

BP1

BP2

PVS1

BP5

BP7

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.991A>C (p.Ser331Arg) is a missense variant which is absent from gnomAD v2 and v3 (PM2_Supporting). The computational predictor REVEL gives a score of 0.106, and the splice site predictor SpliceAI indicated no impact on splicing, evidence that does not predict a damaging effect on RUNX1 function (BP4). In summary, this variant meets the criteria to be classified as a VUS for autosomal dominant hereditary thrombocytopenia and hematologic cancer predisposition syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy VCEP: PM2_Supporting and BP4.

Met criteria codes

PM2_Supporting			Completely absent from gnomAD with a mean coverage of at least 20X (v2 and v3).
BP4			REVEL score = 0.106, which is less than the v2 threshold of 0.50. SpliceAI doesn't predict any significant splicing impact (Δ scores $\leq$ 0.20).

Not Met criteria codes

PS1			No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PS2			No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PS3			No literature was found in LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PS4			No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
BA1			Completely absent from gnomAD with a mean coverage of at least 20X (v2 and v3).
PP1			No literature was found in LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PP2			Not applicable
PP3			REVEL score = 0.106, which is not higher than the v2 threshold of 0.88. SpliceAI doesn't predict any significant splicing impact (Δ scores $\leq$ 0.20).
PP4			Not applicable
PM1			Not located at a hotspot (R107, K110, A134, R162, R166, S167, R169, G170, K194, T196, D198, R210, R204) or within residues 89-204.
PM3			Not applicable
PM5			S331N/S304R has been reported in Mastermind, but not frequently enough to suggest pathogenicity.

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