

Variant: NM_001754.5(RUNX1):c.258G>A (p.Pro86=)

Version: 1.0

CA320642685 [↗](#)

1007447 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 8520e779-0fdc-4c15-989a-682dc4e1c6e6

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HGVS expressions

NM_001754.5(RUNX1):c.258G>A (p.Pro86=)

NM_001754.5:c.258G>A

NC_000021.9:g.34886936C>T

CM000683.2:g.34886936C>T

NC_000021.8:g.36259233C>T

CM000683.1:g.36259233C>T

NC_000021.7:g.35181103C>T

NG_011402.2:g.1102776G>A

ENST00000675419.1:c.258G>A

ENST00000300305.7:c.258G>A

ENST00000344691.8:c.177G>A

ENST00000358356.9:c.177G>A

ENST00000399237.6:c.222G>A

ENST00000399240.5:c.177G>A

ENST00000437180.5:c.258G>A

ENST00000455571.5:c.219G>A

ENST00000482318.5:c.59-6223G>A

NM_001001890.2:c.177G>A

NM_001122607.1:c.177G>A

NM_001754.4:c.258G>A

NM_001001890.3:c.177G>A

NM_001122607.2:c.177G>A

Likely Benign

Met criteria codes **2**

BP4 BP7

Not Met criteria codes **21**

PS1 PS3 PS4 BA1 PP1 PP2
PP3 PP4 PM1 PM3 PM5
PM4 PM2 BS1 BS4 BS3
BP3 BP1 BP2 PVS1 BP5

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

Myeloid Malignancy VCEP

NM_001754.5:c.258G>A (p.Pro86=) is a synonymous variant which is not predicted by SpliceAI to impact splicing. In addition, it occurs at a nucleotide that is not conserved as shown by its phyloP score (BP4, BP7). The germline variant has not been reported in patients meeting the RUNX1 phenotypic criteria and has been identified at an overall minor allele frequency of 0.0077% (1/13002 alleles) in ESP. In summary, this variant meets the criteria to be classified as likely benign for hereditary thrombocytopenia and hematologic cancer predisposition syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy VCEP: BP4, BP7.

Met criteria codes

BP4			SpliceAI doesn't predict any significant splicing impact (Δ scores $\leq$ 0.20).
BP7			This synonymous variant is predicted by MES and SpliceAI to lead to either no change/an increase/a decrease by no more than 10% in the canonical splice site score and no putative cryptic splice sites are created (SSF-like predicts the creation of a cryptic donor splice site at c.259). An evolutionary conservation algorithm predicts the site as being weakly conserved (PhyloP score = -3.22807 in GRCh38), but the variant allele is not the reference nucleotide in one primate and/or three mammal species.

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No relevant data found in literature search, including 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), but is present in 1/6501 individuals in ESP.
PP1			No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PP2			Not applicable
PP3			SpliceAI doesn't predict any significant splicing impact (Δ scores $\leq$ 0.20).
PP4			Not applicable
PM1			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline			
PM3		✖	Not applicable
PM5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✖	Completely absent from gnomAD with a mean coverage of at least 20X (v2 and v3), but is present in 1/6501 individuals in ESP.
BS1		✖	Completely absent from gnomAD with a mean coverage of at least 20X (v2 and v3), but is present in 1/6501 individuals in ESP.
BS4		✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
BS3		✖	No relevant data found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
BP3		✖	Not applicable
BP1		✖	Not applicable
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	Not applicable

Curation History

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