

Variant: *NM_001754.4(RUNX1):c.973C>T (p.Pro325Ser)*

Version: 1.0

CA10014230 [↗](#)

651472 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: be94fc5f-d697-4b41-92ca-de27c51dcf76

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HGVS expressions

NM_001754.4:c.973C>T

NM_001754.4(RUNX1):c.973C>T (p.Pro325Ser)

NC_000021.9:g.34792605G>A

CM000683.2:g.34792605G>A

NC_000021.8:g.36164902G>A

CM000683.1:g.36164902G>A

NC_000021.7:g.35086772G>A

NG_011402.2:g.1197107C>T

ENST00000675419.1:c.973C>T

ENST00000300305.7:c.973C>T

ENST00000344691.8:c.892C>T

ENST00000399240.5:c.700C>T

ENST00000437180.5:c.973C>T

ENST00000482318.5:c.*563C>T

NM_001001890.2:c.892C>T

NM_001001890.3:c.892C>T

NM_001754.5:c.973C>T

Uncertain Significance

Met criteria codes **2**

BP4

PS4_Supporting

Not Met criteria codes **24**

BS2

PVS1

BS1

BS4

BS3

BP5

BP7

BP3

BP1

BP2

PS1

PS2

PS3

BA1

PP1

PP2

PP3

PP4

PM6

PM2

PM1

PM3

PM5

PM4

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_001754.4(RUNX1):c.973C>T (p.Pro325Ser) is a missense variant which is absent from gnomAD v2, but has a highest population minor allele frequency of 0.006543% (1/15284 alleles) in the African American/African population from gnomAD v3. This variant is not published, and out of 19 carriers reported in clinical laboratories, only one was diagnosed with MDS in their 40s and is a confirmed germline carrier (PS4_supporting). The computational predictor REVEL gives a score of 0.05, which is below the threshold of 0.50, and the splice site predictor SpliceAI indicated that the variant has 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 variant of uncertain significance (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: PS4_supporting and BP4.

Met criteria codes

BP4			REVEL score = 0.05, which is lower than the v2 threshold of 0.50. No splicing impact predicted by SpliceAI (Δ scores $\leq$ 0.20).
PS4_Supporting			The variant has not been published in the literature or databases, but has been identified in the germline (unaffected child is also a carrier) of a patient who developed MDS in their 40s. It has also been reported in clinical laboratories in patients with unrelated cancer diagnoses or where germline origin could not be confirmed (one patient being evaluated for SCID/CID/Cytopenias).

Not Met criteria codes

BS2			Not applicable
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			gnomAD v2: absent from database with a mean coverage of at least 20x gnomAD v3: ALL: 0.0006573% (1/152134 alleles) - AMR: 0.006543% (1/15284 alleles)
BS4			The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
BS3			The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
BP5			Not applicable
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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			
PS1		✖	The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
PS2		✖	The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
PS3		✖	The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
BA1		✖	gnomAD v2: absent from database with a mean coverage of at least 20x gnomAD v3: ALL: 0.0006573% (1/152134 alleles) - AMR: 0.006543% (1/15284 alleles)
PP1		✖	The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
PP2		✖	Not applicable
PP3		✖	REVEL score = 0.05, which is not higher than the v2 threshold of 0.88.
PP4		✖	Not applicable
PM6		✖	The variant has not been reported in the literature, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar.
PM2		✖	gnomAD v2: absent from database with a mean coverage of at least 20x gnomAD v3: ALL: 0.0006573% (1/152134 alleles) - AMR: 0.006543% (1/15284 alleles)
PM1		✖	The variant is not present at a hotspot or in the critical region of the runt homology domain.
PM3		✖	Not applicable
PM5		✖	Other variants at P325 or P298 were not found in HGMD, COSMIC, or Mastermind.
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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