

Variant: *NM_001754.4(RUNX1):c.1163C>A (p.Ser388Ter)*

Version: 1.1

[CA410147908](#)

[561222 \(ClinVar\)](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 37cf5142-fd3f-4896-9da9-ca4c54b542ea

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HGVS expressions

NM_001754.4:c.1163C>A

NM_001754.4(RUNX1):c.1163C>A (p.Ser388Ter)

NC_000021.9:g.34792415G>T

CM000683.2:g.34792415G>T

NC_000021.8:g.36164712G>T

CM000683.1:g.36164712G>T

NC_000021.7:g.35086582G>T

NG_011402.2:g.1197297C>A

ENST00000675419.1:c.1163C>A

ENST00000300305.7:c.1163C>A

ENST00000344691.8:c.1082C>A

ENST00000399240.5:c.890C>A

ENST00000437180.5:c.1163C>A

ENST00000482318.5:c.*753C>A

NM_001001890.2:c.1082C>A

NM_001001890.3:c.1082C>A

NM_001754.5:c.1163C>A

Likely Pathogenic

Met criteria codes 4

PS4_Supporting

PVS1_Strong

PS3_Supporting

PM2_Supporting

Not Met criteria codes 22

PS1

PS2

BA1

PP1

PP2

PP3

PP4

PM6

PM1

PM3

PM5

PM4

BS2

BS1

BS4

BS3

BP4

BP3

BP1

BP2

BP5

BP7

Evidence Links 1

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

The NM_001754.4:c.1163C>A (p.Ser388Ter) variant is a nonsense variant that is predicted to introduce a premature stop codon and expected to result in nonsense-mediated mRNA decay (PVS1). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). Transactivation assays demonstrate enhanced transactivation (>115% of wt) (PS3_Supporting; PMID: 20846103). This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_Supporting; PMID: 20846103). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PVS1, PM2_supporting, PS3_Supporting, PS4_Supporting.


























Met criteria codes

PS4_Supporting			One affected proband from PMID: 20846103. <hr/> 1 affected proband with MDS and her mother has AML. PubMed:20846103 
PVS1_Strong			Nonsense variant after the c.916 cutoff that do not predict to undergo NMD. But the truncated region of RUNX1 is critical to protein function.
PS3_Supporting			Transactivation assay demonstrating moderately altered transactivation (>115% of WT). <hr/> Functional activity of our RUNX1 mutant was tested using a luciferase assay [Figure 1(D)]. The mutant demonstrated a significant increase in trans- activation when compared to wild-type RUNX1. PubMed:20846103 
PM2_Supporting			The variant is absent from all population databases.

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			Three affected individuals in one pedigree with 2 meioses from PMID: 20846103. <hr/> 3 affected individuals in one pedigree with 2 meioses. PubMed:20846103 
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			3 affected individuals in one pedigree with 2 meioses. PubMed:20846103 
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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