

Variant: *NM_001754.5(RUNX1):c.593A>T (p.Asp198Val)*

Version: 1.2

CA410207972 [↗](#)

627342 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 05236ec3-500a-4994-b830-31e58ed86bfb

Approved on: Mon, 05 Oct 2026 00:00:00 +0000

Published on: Mon, 05 Oct 2026 00:00:00 +0000

HGVS expressions

NM_001754.5(RUNX1):c.593A>T (p.Asp198Val)

NM_001754.5:c.593A>T

NC_000021.9:g.34859494T>A

CM000683.2:g.34859494T>A

NC_000021.8:g.36231791T>A

CM000683.1:g.36231791T>A

NC_000021.7:g.35153661T>A

NG_011402.2:g.1130218A>T

ENST00000675419.1:c.593A>T

ENST00000300305.7:c.593A>T

ENST00000344691.8:c.512A>T

ENST00000358356.9:c.512A>T

ENST00000399237.6:c.557A>T

ENST00000399240.5:c.512A>T

ENST00000437180.5:c.593A>T

ENST00000467577.1:n.85A>T

ENST00000482318.5:c.*183A>T

NM_001001890.2:c.512A>T

NM_001122607.1:c.512A>T

NM_001754.4:c.593A>T

NM_001001890.3:c.512A>T

NM_001122607.2:c.512A>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PS4_Moderate

PP3

PM1_Strong

Not Met criteria codes 22

BS1

BS4

BS3

BS2

PVS1

BP5

BP7

BP4

BP3

BP1

BP2

PS1

PS2

PS3

BA1

PP1

PP2

PP4

PM6

PM3

PM5

PM4

Evidence Links 3

Expert Panel

[Myeloid Malignancy VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Myeloid Malignancy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RUNX1 Version 3.1

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Myeloid Malignancy VCEP

NM_001754.4:c.593A>T (p.Asp198Val) is a missense variant which affects one of the hotspot residues (Asp198) within the RHD (amino acids 89-204; PM1_Strong). This variant has a REVEL score ≥ 0.88 (0.96) (PP3) and is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting). This variant has been reported in two probands meeting at least one of the RUNX1-phenotypic criteria (PS4_Moderate; PMID: 27479822). In summary, this variant meets the criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1_Strong, PP3, PM2_Supporting, PS4_Moderate.

Met criteria codes

PM2_Supporting			This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).
PS4_Moderate			2 probands meeting RUNX1-phenotypic criteria (PMID: 27479822; Internal laboratory data).
			Somatic mutation from bone marrow cells. PubMed:17485549 
			Somatic mutation from tumor cells. PubMed:17650443 
			Family 18-I with thrombocytopenia PubMed:27479822 
PP3			REVEL score: 0.959 > 0.88.
PM1_Strong			This variant affects the following hotspot residue within the RHD: D198 (PM1_strong).

Not Met criteria codes

BS1			This variant does not have a MAF between 0.00015 (0.015%) and 0.0015 (0.15%) in any general continental dataset.
BS4			Segregation was not found to be absent in two or more informative meioses.
BS3			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.
PVS1			This variant is not a null variant.
BP5			This rule is not applicable for MM-VCEP.
BP7			This variant is not a synonymous or intronic variant.

BP4			This missense variant does not have a REVEL score < 0.50.
BP3			This rule is not applicable for MM-VCEP.
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			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.
PS1			There has not yet been a missense change resulting in the same change in protein which has been determined to be pathogenic at this amino acid residue.
PS2			De novo data for this variant has not been reported in literature.
PS3			In vitro or in vivo functional data has not been reported for this variant in the literature.
BA1			This variant does not have a MAF $\geq$ 0.0015 (0.15%) in any general continental population dataset.
PP1			1 meiosis from internal laboratory data.
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			This rule is not applicable for MM-VCEP.
PM6			De novo data for this variant has not been reported in literature.
PM3			This rule is not applicable for MM-VCEP.
PM5			This variant is a missense change at the same residue (p. D198) where a different missense change has been previously established as a likely pathogenic variant (ClinVar ID 561251, 2665098) based on MM-VCEP rules for RUNX1 and RNA data or agreement in splicing predictors (SSF and MES) show no splicing effects. PM5_supporting cannot be met since PM1_strong is met.
PM4			This variant is not an in-frame deletion/insertion.

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