

Variant: NM_001754.5(RUNX1):c.593A>C (p.Asp198Ala)

Version: 1.0

CA410207974 [↗](#)

561251 (ClinVar) [↗](#)

Gene: RUNX1 (HGNC:861)

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 9e51dbad-5cbe-4a99-8a12-f7daf29fd7ab

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HGVS expressions

NM_001754.5:c.593A>C

NM_001754.5(RUNX1):c.593A>C (p.Asp198Ala)

NC_000021.9:g.34859494T>G

CM000683.2:g.34859494T>G

NC_000021.8:g.36231791T>G

CM000683.1:g.36231791T>G

NC_000021.7:g.35153661T>G

NG_011402.2:g.1130218A>C

ENST00000675419.1:c.593A>C

ENST00000300305.7:c.593A>C

ENST00000344691.8:c.512A>C

ENST00000358356.9:c.512A>C

ENST00000399237.6:c.557A>C

ENST00000399240.5:c.512A>C

ENST00000437180.5:c.593A>C

ENST00000467577.1:n.85A>C

ENST00000482318.5:c.*183A>C

NM_001001890.2:c.512A>C

NM_001122607.1:c.512A>C

NM_001754.4:c.593A>C

NM_001001890.3:c.512A>C

NM_001122607.2:c.512A>C

Likely Pathogenic

Met criteria codes 5

PS4_Supporting PP3 PM1

PM5_Supporting PM2_Supporting

Not Met criteria codes 21

BS2 BS1 BS4 BS3 BP5 BP7

BP4 BP3 BP1 BP2 PS1 PS2

PS3 BA1 PP1 PP2 PP4

PM3 PM4 PM6 PVS1

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(RUNX1):c.593A>C (p.Asp198Ala) is a missense variant. This variant is completely absent from all population databases with at least 20x coverage for RUNX1 in gnomAD v2.1.1 and v3.1.2 (PM2_supporting). This variant affects an amino acid residue within the RHD domain that is defined as a mutational hotspot by the ClinGen MM-VCEP (PM1). The REVEL score is ≥ 0.88 (0.962) (PP3). Two other missense variants (c.593A>T, p.Asp198Val, ClinVar Variation ID 627342 and c.592G>T (p.Asp198Tyr), CA410207975) in the same codon has been classified as likely pathogenic for Hereditary thrombocytopenia and hematologic cancer predisposition syndrome by the ClinGen MMVCEP (PM5_Supporting). This variant has been reported in a proband with AML, meeting RUNX1-phenotypic criteria (PS4_supporting, internal data from PreventionGenetics). In summary, the clinical significance of this variant is likely pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1, PM2_supporting, PP3, PM5_supporting, PS4_supporting.

Met criteria codes

PS4_Supporting			Answer from the lab who submitted the variant in Clinvar (PreventionGenetics) : Our patient had AML, a personal and family history of familial thrombocytopenia, easy bruising, and hypocellular marrow at diagnosis. The individual's mother also carried the variant and had thrombocytopenia. Although they were unavailable for testing, the maternal grandmother and great-grandfather also were reported to have easy bruising. The maternal great-grandfather died of leukemia in his 60s.
PP3			This missense variant has a REVEL score ≥ 0.88 (0.962) (PP3). SpliceAI score is null.
PM1			This variant affects an amino acid residue within the RHD domain that is defined as a mutational hotspot by the ClinGen MM-VCEP (PM1)
PM5_Supporting			Two other missense variants (c.593A>T, p.Asp198Val, ClinVar Variation ID 627342 and c.592G>T (p.Asp198Tyr), CA410207975) in the same codon has been classified as likely pathogenic for Hereditary thrombocytopenia and hematologic cancer predisposition syndrome by the ClinGen MMVCEP (PM5_Supporting).
PM2_Supporting			This variant is completely absent from all population databases with at least 20x coverage for RUNX1 in gnomAD v2.1.1 and v3.1.2 (PM2_supporting).

Not Met criteria codes

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			Clinvar has one entry for this variant but the affected status is unknown. To our knowledge, no publication has reported this variant to date.
BS3			

			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			This rule is not applicable to the MMVCEP.
BP7			This is a missense variant.
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			This rule is not applicable to the MMVCEP.
BP1			This rule is not applicable to the MMVCEP.
BP2			To our knowledge, no publication has reported this variant to date.
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			To our knowledge, no publication has reported this variant to date.
PS3			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			Answer from the lab who submitted the variant in Clinvar (PreventionGenetics) : Our patient had AML, a personal and family history of familial thrombocytopenia, easy bruising, and hypocellular marrow at diagnosis. The individual's mother also carried the variant and had thrombocytopenia. Although they were unavailable for testing, the maternal grandmother and great-grandfather also were reported to have easy bruising. The maternal great-grandfather died of leukemia in his 60s. ==> 2 meioses with positive genotype instead of 3.
PP2			This rule is not applicable to the MMVCEP.
PP4			This rule is not applicable to the MMVCEP.
PM3			This rule is not applicable to the MMVCEP.
PM4			This variant is a missense.
PM6			To our knowledge, no publication has reported this variant to date.

PVS1



This is a missense variant.

Curation History [↗](#)

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