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
Approved on: 2023-12-09
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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

PM1 PM5_Supporting PM2_Supporting PS4_Supporting PP3

Not Met criteria codes 21

PM6 PM3 PM4 PVS1 BA1 BS4 BS3 BS1 BS2 BP5 BP7 BP2 BP3 BP4 BP1 PS1 PS2 PS3 PP4 PP1 PP2

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*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

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

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).
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.

Not Met criteria codes

PM6	✖	To our knowledge, no publication has reported this variant to date.
PM3	✖	This rule is not applicable to the MMVCEP.
PM4	✖	This variant is a missense.
PVS1	✖	This is a missense variant.

BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	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
BP5		✖	This rule is not applicable to the MMVCEP.
BP7	ℹ	✖	This is a missense variant.
BP2	ℹ	✖	To our knowledge, no publication has reported this variant to date.
BP3		✖	This rule is not applicable to the MMVCEP.
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	This rule is not applicable to the MMVCEP.
PS1	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4		✖	This rule is not applicable to the MMVCEP.
PP1	ℹ	✖	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.

Curation History

Showing 1 to 1 of 1 rows