The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001754.5(RUNX1):c.586A>G (p.Thr196Ala)

Version: 1.1

CA410207987

988811 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: d5ad94ce-5501-4361-a280-2142d4eed57a
Approved on: Mon, 05 Oct 2026 00:00:00 +0000
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HGVS expressions

NM_001754.5(RUNX1):c.586A>G (p.Thr196Ala)
NM_001754.5:c.586A>G
NC_000021.9:g.34859501T>C
CM000683.2:g.34859501T>C
NC_000021.8:g.36231798T>C
CM000683.1:g.36231798T>C
NC_000021.7:g.35153668T>C
NG_011402.2:g.1130211A>G
ENST00000675419.1:c.586A>G
ENST00000300305.7:c.586A>G
ENST00000344691.8:c.505A>G
ENST00000358356.9:c.505A>G
ENST00000399237.6:c.550A>G
ENST00000399240.5:c.505A>G
ENST00000437180.5:c.586A>G
ENST00000467577.1:n.78A>G
ENST00000482318.5:c.*176A>G
NM_001001890.2:c.505A>G
NM_001122607.1:c.505A>G
NM_001754.4:c.586A>G
NM_001001890.3:c.505A>G
NM_001122607.2:c.505A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM1_Strong PM2_Supporting PS4_Moderate

Not Met criteria codes 22

PP1 PP2 PP4 PM3 PM5 BA1 PM4 PM6 BS2 BS1 BS4 BS3 PS1 PS2 PS3 BP4 BP3 BP1 BP2 PVS1 BP5 BP7

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 for RUNX1 Version 3.1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.4:c.586A>G (p.Thr196Ala) is a missense variant which affects one of the hotspot residues (Thr196) 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; PMIDs: 27479822, 31698193). 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_Supporting.

Met criteria codes

PP3	✔	This missense variant has a REVEL score >0.88(0.957) and does not have any splicing effects (SpliceAI Score : 0.00)
PM1_Strong	✔	This variant affects one of the hotspot residues established by the MM-VCEP for RUNX1
PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1
PS4_Moderate	✔	This variant has been reported in two probands meeting at least one of the RUNX1-phenotypic criteria (PS4_ Supporting; PMID: 27479822, SCV001450794.1, PMID: 31698193).

Not Met criteria codes

PP1	✖	This variant was not found to co-segregate with disease in multiple affected family members.
PP2	✖	This rule is not applicable for MM-VCEP
PP4	✖	This rule is not applicable for MM-VCEP
PM3	✖	This rule is not applicable for MM-VCEP
PM5	✖	This variant is a missense change at the same residue (p.Thr196) where a different missense change has been previously reported as a pathogenic variant (PMID: 34233450, p.(Thr196Ile), p.(Thr196Arg)) based on MM-VCEP rules for RUNX1and RNA data or agreement in splicing predictors (SSF and MES) show no splicing effects. PM5 cannot be applied at this stage as these variants still need to be recognized as pathogenic by MM-VCEP.
BA1	✖	This variant is completely absent from all population databases with at least 20x coverage for RUNX1
PM4	✖	Not applicable as this is a Missense variant
PM6	✖	This variant has not been reported in probands in the literature.

BS2		✖	This variant is completely absent in gnomAD
BS1	ℹ	✖	This variant is completely absent from all population databases with at least 20x coverage for RUNX1
BS4	ℹ	✖	This variant has not been reported in affected family members.
BS3	ℹ	✖	No functional data found
PS1	ℹ	✖	The same amino acid change has not been reported as pathogenic at this residue.
PS2		✖	This variant has not been reported in probands in the literature.
PS3	ℹ	✖	No functional data found
BP4	ℹ	✖	This missense variant has a REVEL score >0.88(0.957) and does not have any splicing effects (SpliceAI Score : 0.00)
BP3		✖	This rule is not applicable for MM-VCEP
BP1		✖	This rule is not applicable for MM-VCEP
BP2	ℹ	✖	Variant is absent in gnomAD and no homozygotes present with pathogenic variant inheritance pattern
PVS1	ℹ	✖	This is a missense variant and PVS1 is only applied for null variants therefore this rule would not apply
BP5		✖	This rule is not applicable for MM-VCEP
BP7	ℹ	✖	Not a synonymous variant therefore cannot be applied

Curation History

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