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.400G>C (p.Ala134Pro)

Version: 1.2

CA248623

14468 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: d5e03ae0-3ff2-428d-87e3-ae93412f6bf1
Approved on: 2026/5/27
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HGVS expressions

NM_001754.5:c.400G>C
NM_001754.5(RUNX1):c.400G>C (p.Ala134Pro)
NC_000021.9:g.34880665C>G
CM000683.2:g.34880665C>G
NC_000021.8:g.36252962C>G
CM000683.1:g.36252962C>G
NC_000021.7:g.35174832C>G
NG_011402.2:g.1109047G>C
ENST00000675419.1:c.400G>C
ENST00000300305.7:c.400G>C
ENST00000344691.8:c.319G>C
ENST00000358356.9:c.319G>C
ENST00000399237.6:c.364G>C
ENST00000399240.5:c.319G>C
ENST00000437180.5:c.400G>C
ENST00000455571.5:c.361G>C
ENST00000482318.5:c.107G>C
NM_001001890.2:c.319G>C
NM_001122607.1:c.319G>C
NM_001754.4:c.400G>C
NM_001001890.3:c.319G>C
NM_001122607.2:c.319G>C

Pathogenic

Met criteria codes 6

PM2_Supporting PS3 PS4_Supporting PP1 PP3 PM1_Strong

Not Met criteria codes 20

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

Evidence Links 2

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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.4:c.400G>C (p.Ala134Pro) is a missense variant which affects one of the hotspot residues (A134) within the RHD (PM1_Strong). Transactivation assays demonstrate altered transactivation (<20% of wt) and data from secondary assays demonstrate altered CBFβ binding and sub-cellular localization (PS3; PMID: 23848403). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting) and has a REVEL score of >0.75 (0.95) (PP3). This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_ Supporting; PMID: 12060124) and was found to co-segregate with disease in multiple affected family members, with three meioses observed in one family (PP1; PMID: 12060124). In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1_Strong, PS3, PM2_Supporting, PP3, PS4_Supporting, PP1.

Met criteria codes

PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).
PS3	✔	Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered CBFβ binding and sub-cellular localization (PMID:23848403) (PS3). Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered CBFβ binding and sub-cellular localization. **PubMed:23848403**
PS4_Supporting	✔	One family with thrombocytopenia and acute myeloid leukemia (PS4_supporting). One family with thrombocytopenia and acute myeloid leukemia. **PubMed:12060124**
PP1	✔	3 meioses in a family with thrombocytopenia and acute myeloid leukaemia (PP1). 3 meioses in a family with thrombocytopenia and acute myeloid leukaemia. **PubMed:12060124**
PP3	✔	This missense variant has a REVEL score ≥ 0.88 (0.945) (PP3).
PM1_Strong	✔	This variant affects one of the following hotspot residues within the RHD: A134 (PM1).

Not Met criteria codes

PVS1	✖	This variant is not a null variant.
BS2	✖	This rule is not applicable for MM-VCEP.
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 meiosis. 3 meioses in a family with thrombocytopenia and acute myeloid leukaemia. PubMed:12060124
BS3	✖	This variant has not been featured in in vitro or in vivo functional studies that show no damaging effect on protein function or splicing.
BP4	✖	This missense variant does not have a REVEL score < 0.50.
BP3	✖	This rule is not applicable for MM-VCEP.
BP1	✖	This rule is not applicable for MM-VCEP.
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.
BP5	✖	This rule is not applicable for MM-VCEP.
BP7	✖	This variant is not a synonymous or intronic variant.
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.
PM3	✖	This rule is not applicable for MM-VCEP.
PM5	✖	This variant is a missense change at the same residue (p.A134) where a different missense change has been previously established as a likely pathogenic variant (ClinVar ID 1484777) based on MM-VCEP rules for RUNX1 and RNA data or agreement in splicing predictors (SSF and MES) show no splicing effects. However, PM5_supporting cannot be applied since PM1_strong is met.
PM4	✖	This variant is not an in-frame deletion/insertion.
BA1	✖	This variant does not have a MAF ≥ 0.0015 (0.15%) in any general continental population dataset.
PM6	✖	De novo data for this variant has not been reported in literature.
PP2	✖	This rule is not applicable for MM-VCEP.

PP4	✖	This rule is not applicable for MM-VCEP.

Curation History

Showing 1 to 3 of 3 rows

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