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.1198_1201dup (p.Pro401fs)

Version: 1.2

CA658824658

561223 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9aa88b89-e4e4-4fa5-aca4-4ce8f0b31372
Approved on: Thu, 15 Oct 2026 00:00:00 +0000
Published on: Thu, 15 Oct 2026 00:00:00 +0000

HGVS expressions

NM_001754.5(RUNX1):c.1198_1201dup (p.Pro401fs)
NM_001754.5:c.1198_1201dup
NC_000021.9:g.34792379_34792382dup
CM000683.2:g.34792379_34792382dup
NC_000021.8:g.36164676_36164679dup
CM000683.1:g.36164676_36164679dup
NC_000021.7:g.35086546_35086549dup
NG_011402.2:g.1197332_1197335dup
ENST00000675419.1:c.1198_1201dup
ENST00000300305.7:c.1198_1201dup
ENST00000344691.8:c.1117_1120dup
ENST00000399240.5:c.925_928dup
ENST00000437180.5:c.1198_1201dup
ENST00000482318.5:c.*788_*791dup
NM_001001890.2:c.1117_1120dup
NM_001754.4:c.1198_1201dup
NM_001001890.3:c.1117_1120dup

Likely Pathogenic

Met criteria codes 3

PVS1_Strong PM2_Supporting PM5_Supporting

Not Met criteria codes 23

PM6 PM1 PM3 PM4 BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PS3 PS4 PP1 PP2 PP3 PP4

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**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.5(RUNX1):c.1198_1201dup (p.Pro401LeufsTer?) is a frameshift variant which is not predicted to undergo NMD (PVS1_Strong). This variant is downstream of c.98 (PM5_Supporting) and is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PVS1_Strong, PM5_Supporting, PM2_Supporting.

Met criteria codes

PVS1_Strong	✔	Duplication that is not expected to result in NMD, but is expected to alter the transactivation domain, inhibitory domain, and/or the VWRPY motif, as well as elongate the protein.
PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).
PM5_Supporting	✔	This variant is a frameshift variant that is downstream of c.98 (PM5_Supporting).

Not Met criteria codes

PM6	✖	De novo data for this variant has not been reported in literature.
PM1	✖	This variant is not a missense variant.
PM3	✖	Not applicable
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.
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 data for this variant has not been reported in literature.
BS3	✖	This variant has not been featured in in vitro or in vivo functional studies showing a damaging effect on the gene or gene product.

“Of the 28 frameshift mutations, 7 generated truncated peptides with complete or partial deletion of the RHD, 4 generated truncated peptides with intact RHD region, and the remaining 17 generated elongated proteins with intact RHD region (Figure 1); all were suggested to abolish transactivation potential resulting from complete or partial loss of TAD,34 with the exception of P375fsX570, which retained the intact TAD.” **PubMed:19808697**
“The C-terminal frameshift mutants all displayed strong interaction with DNA and CBFβ, but only weak activities on C-FMS induction, except the Asp424Glyfs*149 mutant which does not affect the TAD. The dominant-negative effects of these C-terminal frameshift mutants were demonstrated by Harada and colleagues previously (2, 10), and our data were consistent with their observation.” **PubMed:25840971**

"All of the C-terminal mutations (cases 24-32) [(24-31 in patients with sporadic MDS and 1 patient with secondary MDS)] resulted in frame shifts similar to the Runx2 mutations identified in CCD [(Fig. 7)]... Analysis of C-terminal mutants provided 3 additional types of mutation: attenuated DNA-binding potential without trans-activation potential (Type a-2, mutants 25, 31, and 32), enhanced DNA-binding ability but no trans-activation potential (Type a-3, mutants 24, 26, 27, and 30b), and DNA-binding ability equivalent to wild-type AML1 but no trans-activation potential (Type a-4, mutant 30a) [(Fig. 6)]." PubMed:14615365

BS2		✖	Not applicable
BP5		✖	Not applicable
BP7	ℹ	✖	This variant is not a synonymous or intronic variant.
BP4	ℹ	✖	This variant does not have applicable in-silico data available.
BP3		✖	This rule is not applicable for MM-VCEP.
BP1		✖	Not applicable
BP2	ℹ	✖	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	ℹ	✖	This variant is not a missense, or synonymous variant.
PS2		✖	De novo data for this variant has not been reported in literature.
PS3	ℹ	✖	Although some other C-terminal frameshift alterations (i.e. stop-loss variants) show functional evidence of loss-of-function with a dominant negative effect, specific data for this particular variant was not found. "Of the 28 frameshift mutations, 7 generated truncated peptides with complete or partial deletion of the RHD, 4 generated truncated peptides with intact RHD region, and the remaining 17 generated elongated proteins with intact RHD region (Figure 1); all were suggested to abolish transactivation potential resulting from complete or partial loss of TAD,34 with the exception of P375fsX570, which retained the intact TAD." PubMed:19808697 "The C-terminal frameshift mutants all displayed strong interaction with DNA and CBFβ, but only weak activities on C-FMS induction, except the Asp424Glyfs*149 mutant which does not affect the TAD. The dominant-negative effects of these C-terminal frameshift mutants were demonstrated by Harada and colleagues previously (2, 10), and our data were consistent with their observation." PubMed:25840971 "All of the C-terminal mutations (cases 24-32) [(24-31 in patients with sporadic MDS and 1 patient with secondary MDS)] resulted in frame shifts similar to the Runx2 mutations identified in CCD [(Fig. 7)]... Analysis of C-terminal mutants provided 3 additional types of mutation: attenuated DNA-binding potential without trans-activation potential (Type a-2, mutants 25, 31, and 32), enhanced DNA-binding ability but no trans-activation potential (Type a-3, mutants 24, 26, 27, and 30b), and DNA-binding ability equivalent to wild-type AML1 but no trans-activation potential (Type a-4, mutant 30a) [(Fig. 6)]." PubMed:14615365
PS4	ℹ	✖	No patients have been described in the literature with this variant and a relevant phenotype (i.e. thrombocytopenia, platelet ultrastructural and/or functional defects, or hematological malignancy). However, it has been described in a

patient with a telomere length of <1st percentile; upon follow-up with the authors, Dr. Mary Armanios indicated that the patient also had thrombocytopenia and the cDNA of this variant is c.1198_1201dupTCGC, but the variant has not been confirmed in the germline.

PP1	ℹ	✖	Segregation data for this variant has not been reported in literature.
PP2		✖	Not applicable
PP3	ℹ	✖	This variant does not have applicable in-silico data available.
PP4		✖	Not applicable

Curation History

Showing 1 to 3 of 3 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.