

Variant: *NM_001754.5(RUNX1):c.467C>A (p.Ala156Glu)*

Version: 1.2

CA248628 [↗](#)

14471 (ClinVar) [↗](#)

Gene: RUNX1 ([HGNC:861](#))

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 1023c045-33cc-4c4b-9297-ea4832be8def

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HGVS expressions

NM_001754.5(RUNX1):c.467C>A (p.Ala156Glu)

NM_001754.5:c.467C>A

NC_000021.9:g.34880598G>T

CM000683.2:g.34880598G>T

NC_000021.8:g.36252895G>T

CM000683.1:g.36252895G>T

NC_000021.7:g.35174765G>T

NG_011402.2:g.1109114C>A

ENST00000675419.1:c.467C>A

ENST00000300305.7:c.467C>A

ENST00000344691.8:c.386C>A

ENST00000358356.9:c.386C>A

ENST00000399237.6:c.431C>A

ENST00000399240.5:c.386C>A

ENST00000437180.5:c.467C>A

ENST00000482318.5:c.*57C>A

NM_001001890.2:c.386C>A

NM_001122607.1:c.386C>A

NM_001754.4:c.467C>A

NM_001001890.3:c.386C>A

NM_001122607.2:c.386C>A

Likely Pathogenic

Met criteria codes **5**

PP1_Strong PM1_Supporting

PS4_Supporting PP3

PM2_Supporting

Not Met criteria codes **21**

PVS1 BA1 BP5 BP7 BP4

BP3 BP1 BP2 BS1 BS4 BS3

BS2 PP2 PP4 PS1 PS2 PS3

PM3 PM5 PM4 PM6

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

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Myeloid Malignancy VCEP

NM_001754.5(RUNX1):c.467C>A (p.Ala156Glu) is a missense variant which affects one of the amino acid residues (Ala156) within the RHD (amino acids 89-204; PM1_Supporting). This variant has a REVEL score ≥ 0.88 (0.90) (PP3) and is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting). This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_Supporting; PMID: 19357396, 27112265) and was found to co-segregate with disease in multiple affected family members, with seven meioses observed in one family (PP1_Strong; PMID: 19357396, 27112265). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1_Supporting, PP3, PM2_Supporting, PS4_Supporting, PP1_Strong.

Met criteria codes

PP1_Strong			8 affected individuals in one pedigree with 7 meioses.
<div>The same family (Pedigree B) reported in PMID: 19357396. PubMed:27112265 </div> <div>8 affected individuals in one pedigree (Pedigree 1) with 7 meioses. PubMed:19357396 </div>			
PM1_Supporting			This variant affects one of the other residues (AA 89-204) within the RHD (PM1_Supporting).
PS4_Supporting			1 affected proband in a family with FPD/AML (PMID: 19357396, PMID: 27112265).
<div>The same family (Pedigree B) reported in PMID: 19357396. PubMed:27112265 </div> <div>1 affected proband in a family with FPD/AML (Pedigree 1). PubMed:19357396 </div>			
PP3			This missense variant has a REVEL score ≥ 0.88 (0.906) (PP3).
PM2_Supporting			This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).

Not Met criteria codes

PVS1			This variant is not a null variant.
BA1			This variant does not have a MAF ≥ 0.0015 (0.15%) in any general continental population dataset.
BP5			This rule is not applicable for MM-VCEP.
BP7			This variant is not a synonymous or intronic variant.
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.
BS1		✖	This variant does not have a MAF between 0.00015 (0.015%) and 0.0015 (0.15%) in any general continental dataset.
BS4		✖	<p>Segregation was not found to be absent in two or more informative meioses.</p> <hr/> <p>The same family (Pedigree B) reported in PMID: 19357396. PubMed:27112265 </p> <p>8 affected individuals in one pedigree (Pedigree 1) with 7 meioses. PubMed:19357396 </p>
BS3		✖	In vitro or in vivo functional data has not been reported for this variant in the literature.
BS2		✖	This rule is not applicable for MM-VCEP.
PP2		✖	This rule is not applicable for MM-VCEP.
PP4		✖	This rule is not applicable for MM-VCEP.
PS1		✖	There has not yet been a missense change determined to be pathogenic at this amino acid residue.
PS2		✖	De novo data for this variant has not been reported in literature.
PS3		✖	In vitro or in vivo functional data has not been reported for this variant in the literature.
PM3		✖	This rule is not applicable for MM-VCEP.
PM5		✖	There has not yet been a different missense change determined to be pathogenic at this amino acid residue.
PM4		✖	This variant is not an in-frame deletion/insertion.
PM6		✖	De novo data for this variant has not been reported in literature.

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