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

Version: 1.1

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

PP3 PP1_Strong PS4_Supporting
PM1_Supporting PM2_Supporting

Not Met criteria codes 21

BS2 PVS1 BS1 BS4 BS3
BP4 BP3 BP1 BP2 BP5 BP7
PM3 PM5 PM4 PS1 PS2
PS3 PM6 BA1 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 Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

The NM_001754.4:c.467C>A (p.Ala156Glu) variant was found to co-segregate with disease in multiple affected family members, with seven meioses observed in one family (PP1_Strong; PMID: 19357396, 27112265). It has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_ Supporting; PMID: 19357396, 27112265). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). It affects one of the residues (AA 105-204) within the RHD (PM1_Supporting). This missense variant has a REVEL score >0.75 (0.906) (PP3). 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: PP1_Strong, PM2_supporting, PP3, PM1_Supporting, PS4_Supporting.

Met criteria codes

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

Not Met criteria codes

BS2		✗	This rule is not applicable for MM-VCEP.
PVS1	ⓘ	✗	This variant is not a null variant.
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. The same family (Pedigree B) reported in PMID: 19357396. **PubMed:27112265** 8 affected individuals in one pedigree (Pedigree 1) with 7 meioses. **PubMed:19357396**

BS3	ⓘ	✖	In vitro or in vivo functional data has not been reported for this variant in the literature.
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.
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.
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.
PM6	ⓘ	✖	De novo data for this variant has not been reported in literature.
BA1	ⓘ	✖	This variant does not have a MAF ≥ 0.0015 (0.15%) in any general continental population dataset.
PP2		✖	This rule is not applicable for MM-VCEP.
PP4		✖	This rule is not applicable for MM-VCEP.

Curation History

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