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Variant: NM_001754.5:c.503G>A

Version: 2.1

CA410202475

3367214 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 228d5007-e165-453d-94df-d85cf6abe224
Approved on: Mon, 05 Oct 2026 00:00:00 +0000
Published on: Mon, 05 Oct 2026 00:00:00 +0000

HGVS expressions

NM_001754.5:c.503G>A
NC_000021.9:g.34880562C>T
CM000683.2:g.34880562C>T
NC_000021.8:g.36252859C>T
CM000683.1:g.36252859C>T
NC_000021.7:g.35174729C>T
NG_011402.2:g.1109150G>A
ENST00000675419.1:c.503G>A
ENST00000300305.7:c.503G>A
ENST00000344691.8:c.422G>A
ENST00000358356.9:c.422G>A
ENST00000399237.6:c.467G>A
ENST00000399240.5:c.422G>A
ENST00000437180.5:c.503G>A
ENST00000482318.5:c.*93G>A
NM_001001890.2:c.422G>A
NM_001122607.1:c.422G>A
NM_001754.4:c.503G>A
NM_001001890.3:c.422G>A
NM_001122607.2:c.422G>A

Likely Pathogenic

Met criteria codes 5

PP1 PP3 PS4_Moderate PM2_Supporting PM1_Supporting

Not Met criteria codes 21

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

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_001754.5(RUNX1):c.503G>A (p.Gly168Glu) is a missense variant which affects one of the amino acid residues (Gly168) within the RHD (amino acids 89-204; PM1_Supporting). This variant has a REVEL score ≥ 0.88 (0.98) (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; PMID: 39375928) and was found to co-segregate with disease in three observed meioses in one family (PP1; PMID:39375928). 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_Moderate, PP1.

Met criteria codes

PP1	✔	This variant has been observed in 3 meioses across 1 family (PMID:39375928) (PP1).
PP3	✔	This missense variant has a REVEL score ≥0.50 (0.947) and the SpliceAI score is not ≥0.38 (0.05 Donor Loss 18bp) (PP3)
PS4_Moderate	✔	This variant has been reported in 2 probands meeting at least one of the RUNX1-phenotypic criteria (PS4_ Moderate; PMID: 39375928, internal lab data).
PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting).
PM1_Supporting	✔	This variant affects one of the other residues (AA 89-204) within the RHD (PM1_supporting).

Not Met criteria codes

PS1	✖	Same location 168 seen different amino acid changes and termination as LP however not the same to be PS1 applicable
PS2	✖	No case studies found
PS3	✖	No functional studies found
PP2	✖	This rule is not applicable for MM-VCEP
PP4	✖	This rule is not applicable for MM-VCEP
PM6	✖	No case studies found
PM3	✖	This rule is not applicable for MM-VCEP

PM5		✖	Cannot be applied due to the application of PM1
PM4		✖	Not a frameshift variant
BA1		✖	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting).
BS2		✖	This rule is not applicable for MM-VCEP
PVS1		✖	not a null variant
BS1		✖	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting).
BS4		✖	No case studies found
BS3		✖	No functional studies found
BP5		✖	This rule is not applicable for MM-VCEP
BP7		✖	Not synonymous or intronic variant
BP4		✖	This missense variant has a REVEL score ≥0.50(0.947) and SpliceAI score is not ≥0.38 (0.05 Donor Loss 18bp) (PP3)
BP3		✖	This rule is not applicable for MM-VCEP
BP1		✖	This rule is not applicable for MM-VCEP
BP2		✖	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting).

Curation History

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