Variant: NM_001754.5(RUNX1):c.965del (p.Leu321_Ser322insTer)

Version: 1.0

CA2573157369

1460663 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: ebe7d39f-0b88-4af9-a8d3-5c53ab3d0a9a
Approved on: 2024-09-10
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HGVS expressions

NM_001754.5:c.965del
NM_001754.5(RUNX1):c.965del (p.Leu321_Ser322insTer)
NC_000021.9:g.34799303del
CM000683.2:g.34799303del
NC_000021.8:g.36171600del
CM000683.1:g.36171600del
NC_000021.7:g.35093470del
NG_011402.2:g.1190409del
ENST00000675419.1:c.965del
ENST00000300305.7:c.965del
ENST00000344691.8:c.884del
ENST00000399240.5:c.692del
ENST00000437180.5:c.965del
ENST00000482318.5:c.*555del
NM_001001890.2:c.884del
NM_001754.4:c.965del
NM_001001890.3:c.884del

Likely Pathogenic

Met criteria codes 3

PM5_Supporting PM2_Supporting PVS1_Strong

Not Met criteria codes 22

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

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 Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.5(RUNX1):c.965del (p.Ser322Ter) is a nonsense variant located downstream of c.98 in transcript NM_001754.4 (PM5_Supporting). It is not expected to undergo nonsense-mediated decay, and the resulting frameshift affects positions c.759-c.1440 as per VCEP specifications, which are critical for protein function (PVS1_Strong). This variant 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 for hereditary thrombocytopenia and hematologic cancer predisposition syndrome based on the ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PVS1_strong, PM2_supporting, PM5_supporting.

Met criteria codes

PM5_Supporting	ⓘ	✓	This variant is a nonsense/frameshift variants that is downstream of c.98 (PM5_Supporting).
PM2_Supporting	ⓘ	✓	This variant is absent from gnomAD v.3.1.2 and gnomAD v2.1.1 which have at least 20x coverage for RUNX1 (PM2_supporting).
PVS1_Strong	ⓘ	✓	This variant is not predicted to undergo NMD, and the truncated/altered region is critical for protein function (nonsense c.917-c.1440 as per VCEP specifications) (PVS1_Strong).

Not Met criteria codes

BS2		✗	This rule is not applicable for the MM.VCEP.
BS1	ⓘ	✗	This variant is absent from gnomAD v.3.1.2 and gnomAD v2.1.1 which have at least 20x coverage for RUNX1 (PM2_supporting).
BS4	ⓘ	✗	Segregation data for this variant has not been reported in literature.
BS3	ⓘ	✗	In vitro or in vivo functional data has not been reported for this variant in the literature.
BP4	ⓘ	✗	This variant does not have applicable in-silico data available.
BP3		✗	This rule is not applicable for the MM.VCEP.
BP1		✗	This rule is not applicable for the 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 the MM.VCEP.
BP7	ⓘ	✗	This variant is not a synonymous or intronic variant.

PM1		✖	This variant does not affect any of the following amino acid residues, nor is it located within the RHD: R107, K110, A134, R162, R166, S167, R169, G170, K194, T196, D198, R201, R204 OR within residues 89-204.
PM3		✖	This rule is not applicable for the MM.VCEP.
BA1	ℹ	✖	This variant is absent from gnomAD v.3.1.2 and gnomAD v2.1.1 which have at least 20x coverage for RUNX1 (PM2_supporting).
PM4	ℹ	✖	This variant is not an in-frame deletion/insertion.
PM6	ℹ	✖	De novo data for this variant has not been reported in literature.
PS1	ℹ	✖	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	ℹ	✖	In vitro or in vivo functional data has not been reported for this variant in the literature.
PP1	ℹ	✖	Segregation data for this variant has not been reported in literature.
PP2		✖	This rule is not applicable for the MM.VCEP.
PP3	ℹ	✖	This variant does not have applicable in-silico data available.
PP4		✖	This rule is not applicable for the MM.VCEP.

Curation History ↗

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001754.5(RUNX1):c.965del (p.Leu…	Likely Pathogenic	Hereditary Thrombocytopenia And Hematologic Cancer Predisposition Syndrome	2024-09-10	1.0	ClinGen Myeloid Malignancy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2	RUNX1

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