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Variant: NM_001754.5(RUNX1):c.328A>G (p.Lys110Glu)

Version: 1.2

CA248613

14465 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 37efba9c-0430-4e4f-a3ce-fc8c501d717a
Approved on: 2026/5/27
Published on: 2026/5/27

HGVS expressions

NM_001754.5:c.328A>G
NM_001754.5(RUNX1):c.328A>G (p.Lys110Glu)
NC_000021.9:g.34886866T>C
CM000683.2:g.34886866T>C
NC_000021.8:g.36259163T>C
CM000683.1:g.36259163T>C
NC_000021.7:g.35181033T>C
NG_011402.2:g.1102846A>G
ENST00000675419.1:c.328A>G
ENST00000300305.7:c.328A>G
ENST00000344691.8:c.247A>G
ENST00000358356.9:c.247A>G
ENST00000399237.6:c.292A>G
ENST00000399240.5:c.247A>G
ENST00000437180.5:c.328A>G
ENST00000455571.5:c.289A>G
ENST00000482318.5:c.59-6153A>G
NM_001001890.2:c.247A>G
NM_001122607.1:c.247A>G
NM_001754.4:c.328A>G
NM_001001890.3:c.247A>G
NM_001122607.2:c.247A>G

Pathogenic

Met criteria codes 6

PS3 PP3 PM1_Strong PM2_Supporting PS4_Supporting PP1_Strong

Not Met criteria codes 20

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

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 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.5(RUNX1):c.328A>G (p.Lys110Glu) is a missense variant which affects one of the hotspot residues (K110) within the RHD (PM1_Strong). Transactivation assays demonstrate altered transactivation (<20% of wt) and data from secondary assays demonstrate altered DNA binding, CBFβ binding, and sub-cellular localization (PS3; PMID: 23848403; 17290219; 11830488). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting) and has a REVEL score of >0.75 (0.95) (PP3). This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_supporting; PMID: 11830488) and was found to co-segregate with disease in multiple affected family members, with seven meioses observed across one family (PP1_Strong; PMID: 11830488). In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1_Strong, PS3, PM2_Supporting, PP3, PS4_Supporting, PP1_Strong.

Met criteria codes

PS3	✔	Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered DNA binding, CBFβ binding and sub-cellular localization. Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered DNA binding, CBFβ binding and sub-cellular localization. PubMed:11830488 Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered DNA binding, CBFβ binding and sub-cellular localization. PubMed:23848403 EMSAs confirmed that K83E mutation affected DNA binding quite severely. PubMed:17290219
PP3	✔	This missense variant has a REVEL score ≥ 0.88 (0.953) (PP3).
PM1_Strong	✔	This variant affects the following hotspot residues within the RHD: K110 (PM1_strong).
PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).
PS4_Supporting	✔	1 (compelling) pedigee identified in the literature. 1 (compelling) pedigee identified in the literature. PubMed:11830488
PP1_Strong	✔	In 1 pedigree, 7 meioses observed for LEUKEMIA. 12 meioses if also including "bleeding disorder and/or platelet defect". In 1 pedigree, 7 meioses observed for LEUKEMIA. 12 meioses if also including "bleeding disorder and/or platelet defect". PubMed:11830488

Not Met criteria codes

PS1	ℹ	✖	There has not yet been a missense change resulting in the same change in protein which has been determined to be pathogenic at this amino acid residue.
PS2		✖	De novo data for this variant has not been reported in literature.
PP2		✖	This rule is not applicable for MM-VCEP.
PP4		✖	This rule is not applicable for MM-VCEP.
PM6	ℹ	✖	De novo data for this variant has not been reported in literature.
PM3		✖	This rule is not applicable for MM-VCEP.
PM5	ℹ	✖	This variant is a missense change at the same residue (p.K110) where a different missense change has been previously established as a likely pathogenic variant (ClinVar ID 1518631, 14465) based on MM-VCEP rules for RUNX1 and RNA data or agreement in splicing predictors (SSF and MES) show no splicing effects. However, since PM1_strong is met, PM5_supporting cannot be applied.
PM4	ℹ	✖	This variant is not an in-frame deletion/insertion.
BA1	ℹ	✖	This variant does not have a MAF ≥ 0.0015 (0.15%) in any general continental population dataset.
BS2		✖	This rule is not applicable for MM-VCEP.
PVS1	ℹ	✖	This variant is not a null variant.
BS1	ℹ	✖	This variant does not have a MAF between 0.00015 (0.015%) and 0.0015 (0.15%) in any general continental dataset.
BS4	ℹ	✖	Segregation was not found to be absent in two or more informative meiosis. In 1 pedigree, 7 meioses observed for LEUKEMIA. 12 meioses if also including "bleeding disorder and/or platelet defect". PubMed:11830488
BS3	ℹ	✖	This variant has not been featured in in vitro or in vivo functional studies that show no damaging effect on protein function or splicing.
BP5		✖	This rule is not applicable for MM-VCEP.
BP7	ℹ	✖	This variant is not a synonymous or intronic variant.
BP4	ℹ	✖	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.

Curation History

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