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Variant: NM_001754.5(RUNX1):c.330G>C (p.Lys110Asn)

Version: 2.0

CA410203419

561234 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: c169acf6-7c2b-48f0-82dd-85bb6bde1d1f
Approved on: 2026/5/4
Published on: 2026/5/4

HGVS expressions

NM_001754.5:c.330G>C
NM_001754.5(RUNX1):c.330G>C (p.Lys110Asn)
NC_000021.9:g.34886864C>G
CM000683.2:g.34886864C>G
NC_000021.8:g.36259161C>G
CM000683.1:g.36259161C>G
NC_000021.7:g.35181031C>G
NG_011402.2:g.1102848G>C
ENST00000675419.1:c.330G>C
ENST00000300305.7:c.330G>C
ENST00000344691.8:c.249G>C
ENST00000358356.9:c.249G>C
ENST00000399237.6:c.294G>C
ENST00000399240.5:c.249G>C
ENST00000437180.5:c.330G>C
ENST00000455571.5:c.291G>C
ENST00000482318.5:c.59-6151G>C
NM_001001890.2:c.249G>C
NM_001122607.1:c.249G>C
NM_001754.4:c.330G>C
NM_001001890.3:c.249G>C
NM_001122607.2:c.249G>C

Pathogenic

Met criteria codes 4

PM2_Supporting PS3 PP3 PM1_Strong

Not Met criteria codes 22

PVS1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PS4 PM3 PM5 PM4 BA1 PM6 PP1 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 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.330G>C (p.Lys110Asn) is a missense variant which affects one of the hotspot residues (K110) in the RHD (PM1_strong) and is completely absent from gnomAD v4 with at least 20x coverage (PM2_supporting). This missense variant has a REVEL score ≥ 0.88 (0.884) (PP3), and a transactivation assay using the M-CSF promoter demonstrated altered transactivation (<70% of WT). Data from secondary assays demonstrated altered DNA binding, CBFβ heterodimerization, and nuclear localization (PMID: 10068652, 11830488), and studies of the mutant protein in mouse bone marrow cells demonstrated a decreased ratio of erythroid to myeloid colonies, resulting in immortalization of cells and the accumulation of myeloblasts and dysplastic progenitors (PMID: 17234761)(PS3). 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, PM2_supporting, PP3, PS3.

Met criteria codes

PM2_Supporting	✔	The variant is absent from gnomAD v2+v3+v4 (>20 coverage).
PS3	✔	The variant in a transactivation assay using the M-CSF promoter exhibited a 70% reduction; the mutant protein was also unable to bind DNA whether or or not in the presence of the CBFβ subunit, without affecting CBFβ heterodimerization and nuclear localization (PMID: 10068652; PMID: 11830488). Additional studies of the mutant protein showed that it decreases the ratio of erythroid to myeloid colonies, results in immortalization of cells, and the accumulation of myeloblasts and dysplastic progenitors (PMID: 17234761). K83N was transduced into murine bone marrow via a retroviral vector and resulted in reduced GFP+ cells (median of 14% GFP+ cells), no effect on the lymphoid lineages, reduced ratio of erythroid to myeloid colonies, increased replating efficiencies and immortalization of cells, and the accumulation of myeloblasts and dysplastic progenitors. Finally, K83N with either T161A or T161A+N109D (alterations that reduce CBFβ-binding) did not change replating efficiencies or the amount of accumulation of progenitor cells, suggesting that immortalization is not necessarily due to a dominant-negative effect. PubMed:17234761 K83N was transduced into SC1 murine fibroblasts, and reduction of this variant's mRNA was seen upon transfection with short interfering-RNA (posttranscriptional silencing of target gene). K83N was transduced into HEK293T cells, and reduction of this variant's mRNA was seen upon transfection with short hairpin-RNA (longer-lasting gene silencing). These results were confirmed by RT-PCR and flow cytometry. PubMed:22649608
PP3	✔	REVEL score = 0.884, which is higher than the v2 threshold of 0.88. SpliceAI doesn't predict any significant splicing impact (Δ scores ≤ 0.20). Additional missense predictions are reviewed in PMID: 32958805.
PM1_Strong	✔	This variant affects one of the hotspot residues (K110) established by the MM-VCEP for RUNX1 (PMID: 31648317; PMID: 10404214; PMID: 10620014; PMID: 11257229; PMID: 26010396).

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS2		✖	This rule is not applicable for MM-VCEP
BS1	ℹ	✖	The variant is absent from gnomAD v2+v3+v4 (>20 coverage).
BS4	ℹ	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
BS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	REVEL score = 0.884, which is not less than the v2 threshold of 0.50. SpliceAI doesn't predict any significant splicing impact (Δ scores ≤ 0.20). Additional missense predictions are reviewed in PMID: 32958805.
BP3		✖	Not applicable
BP1		✖	Not applicable
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	Not applicable
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	The c.330G>T variant also results in p.K110N. This variant has at least been reported as a somatic alteration in an AML that also demonstrated LOH at this locus (pure tumor cells were sequenced after sorting) (PMID: 19773259), 2 breast cancers (PMID: 28481359; PMID: 30205045), and a lung adenocarcinoma (PMID: 31844068). It is classified as likely pathogenic by Invitae (ClinVar Variation ID: 1518631); it hasn't completed review by the MM-VCEP, but the rationale for pathogenicity is likely based on the functional data also available for c.330G>C.
PS2		✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PS4	ℹ	✖	The variant of unclear origin has been reported in 4 individuals with AML (PMID: 10068652; PMID: 27288520; PMID: 31772163; PMID: 32696696), and the somatic variant has been reported in an AML (PMID: 29472724), an MDS (PMID: 31772163), and a TCGA bladder cancer (COSMIC ID: COSV55875639/cBioPortal).
PM3		✖	Not applicable
PM5	ℹ	✖	K110E has been classified as pathogenic by the MM-VCEP. However, glutamic acid and asparagine have differing properties. In addition, this is a hotspot residue. Although not directly stated in the current version of the rules, PM5 should conservatively not be applied.
PM4	ℹ	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BA1	✖	The variant is absent from gnomAD v2+v3+v4 (>20 coverage).
PM6	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PP1	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PP2	✖	Not applicable
PP4	✖	Not applicable

Curation History

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