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Variant: NM_001754.5(RUNX1):c.1270T>C (p.Ser424Pro)

Version: 1.0

CA410147564

970259 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4a2f5955-e2f0-466b-92a1-f20b7be3aa1b
Approved on: 2024-11-13
Published on: 2024-11-13

HGVS expressions

NM_001754.5:c.1270T>C
NM_001754.5(RUNX1):c.1270T>C (p.Ser424Pro)
NC_000021.9:g.34792308A>G
CM000683.2:g.34792308A>G
NC_000021.8:g.36164605A>G
CM000683.1:g.36164605A>G
NC_000021.7:g.35086475A>G
NG_011402.2:g.1197404T>C
ENST00000675419.1:c.1270T>C
ENST00000300305.7:c.1270T>C
ENST00000344691.8:c.1189T>C
ENST00000399240.5:c.997T>C
ENST00000437180.5:c.1270T>C
ENST00000482318.5:c.*860T>C
NM_001001890.2:c.1189T>C
NM_001754.4:c.1270T>C
NM_001001890.3:c.1189T>C

Uncertain Significance

Met criteria codes 1

BP4

Not Met criteria codes 25

PVS1 PS1 PS2 PS3 PS4
PP1 PP2 PP3 PP4 PM6
PM2 PM1 PM3 PM5 PM4
BA1 BS1 BS4 BS3 BS2 BP5
BP7 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 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.1270T>C (p.Ser424Pro) is a missense variant predicted to cause the substitution of serine by proline at amino acid 424 (p.S424P). This variant is absent from gnomAD v2, but in gnomAD v3, the highest population minor allele frequency is 0.07016% (4/4276 alleles) in the East Asian population, and in gnomAD v4, it is 2.641% (624/23626 alleles) in the East Asian population. Both frequencies are higher than the overall allele frequency of all disease-causing alleles derived by the ClinGen Myeloid Malignancy-VCEP. However, genomes failed a quality filter (AS_VQSR) in gnomAD v3 and v4, allele balance is heavily skewed, and site quality seems lower compared to some common, known pathogenic variants (BA1 not met). This variant has been reported in a 59-year-old female with thrombocytopenia and a secondary defect, who also carried RUNX1 c.1256T>G (p.Val419Gly) (phasing unclear) and a 2.5 Mb deletion including FLI1, although the germline origin was presumed rather than confirmed by tissue or familial testing (PMID: 32935436). Additionally, one individual in a Japanese family with B-ALL, likely due to PAX5 G183R, was found to carry this variant, while two siblings were negative (PMID: 35902733). Another patient reportedly with hereditary thrombocytopenia and hematological cancer predisposition associated with RUNX1 carried this variant in the germline, but an unspecified number of affected relatives in the family were negative (ClinVar Accession: SCV002515682.3). The variant has also been reported in patients with AML (PMID: 36900179), MDS (PMID: 36932114), and other tumors (PMID: 30239046; PMID: 30246500; PMID: 32943879; PMID: 35626111; PMID: 37160887; PMID: 37994105), though the variant allele fraction mostly suggests somatic origin or artifact (unconfirmed). No relevant functional data are available for this specific missense variant, but in vitro studies have demonstrated that Ser424 is a phosphorylation target of CDK/Cyclin complexes (PMID: 18003885). The computational predictor REVEL gives a score of 0.465, which is below the threshold of 0.50, and the splice site predictor SpliceAI indicates that the variant has no impact on splicing, suggesting it does not predict a damaging effect on RUNX1 function (BP4). In summary, this variant meets the criteria to be classified as a variant of uncertain significance (VUS) for autosomal dominant hereditary thrombocytopenia and hematologic cancer predisposition syndrome. ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy VCEP: BP4.

Met criteria codes

BP4	✔	REVEL score = 0.465, which is less than the v2 threshold of 0.50. SpliceAI doesn't predict any significant splicing impact (Δ scores ≤ 0.20).

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PS2	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PS3	✖	In vitro functional data demonstrated that S424 is a phosphorylation target of CDK/Cyclin complexes (PMID: 18003885).
PS4	✖	The variant has been reported in a 59-year-old female with thrombocytopenia and a secondary defect, who also carried RUNX1 c.1256T>G/p.V419G (phasing unclear) and a 2.5 Mb deletion including FLI1, but germline origin was presumed instead of confirmed by tissue or familial testing (PMID: 32935436). One individual in a Japanese family with B-ALL likely due to PAX5 G183R was also found to carry this variant (2 siblings were negative) (PMID: 35902733). Finally, a patient reportedly with hereditary thrombocytopenia and hematological cancer predisposition associated with RUNX1 carried this variant in the germline (ClinVar Accession: SCV002515682.3). The variant of unclear origin has also been reported in patients with AML (PMID: 36900179), MDS (PMID: 36932114), or other

tumors (PMID: 30239046; PMID: 30246500; PMID: 32943879; PMID: 35626111; PMID: 37160887; PMID: 37994105), but variant allele fraction mostly suggests somatic origin or artifact (unconfirmed).

PP1	ℹ	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PP2		✖	Not applicable
PP3	ℹ	✖	REVEL score = 0.465, which is not higher than the v2 threshold of 0.88. SpliceAI doesn't predict any significant splicing impact (Δ scores ≤ 0.20).
PP4		✖	Not applicable
PM6	ℹ	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PM2		✖	- Completely absent from gnomAD v2 with a mean coverage of at least 20X. - gnomAD (v3): ALL: 0.005515% (8/145058) - EAS: 0.07016% (4/4276) - FIN: 0.03169% (3/9468) - SAS: 0.002501% (1/4114) - AFR: 0.002501% (1/39980) - gnomAD (v4): ALL: 0.5200% (5949/1143942) - EAS: 2.641% (624/23626) - ASJ: 1.677% (363/21644) - RMG: 1.152% (488/42352) - MEAS: 0.9204% (43/4672) - NFE: 0.4675% (3866/826876) - AFR: 0.4474% (283/63252) - AMR: 0.3607% (164/45462) - FIN: 0.1528% (58/37956) - SAS: 0.07769% (60/77232) *Genomes failed a quality filter (AS_VQSR) in gnomAD v3 and v4. *Allele balance is skewed in gnomAD v2 and v3 and site quality metric may be lower than other common (variant seems to be in a GC-rich region), pathogenic variants.
PM1		✖	Not located in a mutational hot spot
PM3		✖	Not applicable
PM5	ℹ	✖	S424A/S397A is the most commonly reported and classified as a VUS by the MM-VCEP. Other S424/S397 variants are reported in COSMIC and/or Mastermind, but not at a high enough frequency that they would be likely classified as LP/P.
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	- Completely absent from gnomAD v2 with a mean coverage of at least 20X. - gnomAD (v3): ALL: 0.005515% (8/145058) - EAS: 0.07016% (4/4276) - FIN: 0.03169% (3/9468) - SAS: 0.002501% (1/4114) - AFR: 0.002501% (1/39980) - gnomAD (v4): ALL: 0.5200% (5949/1143942) - EAS: 2.641% (624/23626) - ASJ: 1.677% (363/21644) - RMG: 1.152% (488/42352) - MEAS: 0.9204% (43/4672) - NFE: 0.4675% (3866/826876) - AFR: 0.4474% (283/63252) - AMR: 0.3607% (164/45462) - FIN: 0.1528% (58/37956) - SAS: 0.07769% (60/77232) *Genomes failed a quality filter (AS_VQSR) in gnomAD v3 and v4. *Allele balance is skewed in gnomAD v2 and v3 and site quality metric may be lower than other common (variant seems to be in a GC-rich region), pathogenic variants.
BS1	ℹ	✖	- Completely absent from gnomAD v2 with a mean coverage of at least 20X. - gnomAD (v3): ALL: 0.005515% (8/145058) - EAS: 0.07016% (4/4276) - FIN: 0.03169% (3/9468) - SAS: 0.002501% (1/4114) - AFR: 0.002501% (1/39980) - gnomAD (v4): ALL: 0.5200% (5949/1143942) - EAS: 2.641% (624/23626) - ASJ: 1.677% (363/21644) -

RMG: 1.152% (488/42352) - MEAS: 0.9204% (43/4672) - NFE: 0.4675% (3866/826876) - AFR: 0.4474% (283/63252) - AMR: 0.3607% (164/45462) - FIN: 0.1528% (58/37956) - SAS: 0.07769% (60/77232) *Genomes failed a quality filter (AS_VQSR) in gnomAD v3 and v4. *Allele balance is skewed in gnomAD v2 and v3 and site quality metric may be lower than other common (variant seems to be in a GC-rich region), pathogenic variants.

BS4	ℹ	✖	A patient reportedly with hereditary thrombocytopenia and hematological cancer predisposition associated with RUNX1 carried this variant in the germline, but an unspecified number of affected relatives in the family were negative (ClinVar Accession: SCV002515682.3).
BS3	ℹ	✖	In vitro functional data demonstrated that S424 is a phosphorylation target of CDK/Cyclin complexes (PMID: 18003885).
BS2		✖	Not applicable
BP5		✖	This rule is not applicable for the MMVCEP
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	Not applicable
BP1		✖	Not applicable
BP2	ℹ	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches. No homozygotes present in gnomAD v2, v3, or v4.

Curation History

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