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Variant: NM_001754.5(RUNX1):c.1270T>G (p.Ser424Ala)

Version: 1.0

CA410147560

988867 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 74c140f1-c10f-401c-9267-169c14eaf92e
Approved on: 2024-11-13
Published on: 2024-11-13

HGVS expressions

NM_001754.5:c.1270T>G
NM_001754.5(RUNX1):c.1270T>G (p.Ser424Ala)
NC_000021.9:g.34792308A>C
CM000683.2:g.34792308A>C
NC_000021.8:g.36164605A>C
CM000683.1:g.36164605A>C
NC_000021.7:g.35086475A>C
NG_011402.2:g.1197404T>G
ENST00000675419.1:c.1270T>G
ENST00000300305.7:c.1270T>G
ENST00000344691.8:c.1189T>G
ENST00000399240.5:c.997T>G
ENST00000437180.5:c.1270T>G
ENST00000482318.5:c.*860T>G
NM_001001890.2:c.1189T>G
NM_001754.4:c.1270T>G
NM_001001890.3:c.1189T>G

Uncertain Significance

Met criteria codes 1

BP4

Not Met criteria codes 25

PP1 PP2 PP3 PP4 PVS1 BS2 BS1 BS4 BS3 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PS3 PS4 BA1 PM6 PM2 PM1 PM3 PM5 PM4

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>G (p.Ser424Ala) is a missense variant predicted to cause the substitution of serine by alanine at amino acid 424 (p.S424A). This variant is absent from gnomAD v2, but in gnomAD v3, the highest population minor allele frequency is 0.1702% (7/4114 alleles) in the South Asian population, and in gnomAD v4, it is 1.053% (255/24222 alleles) in the East Asian population. These frequencies are higher than the overall allele frequency of all disease-causing alleles derived by the ClinGen Myeloid Malignancy-VCEP. However, allele balance in gnomAD v3 and v4 is heavily skewed, and site quality appears lower compared to some common, known pathogenic variants (BA1 not met). Given the frequency in gnomAD, it is not surprising that this variant has been reported in several individuals with relevant phenotypes: a 32-year-old female with thrombocytopenia and a delayed secretion defect (PMID: 32935436), a Chinese patient with newly diagnosed AML (PMID: 34234861), and a Chinese infant with AML (PMID: 35814831). However, the confirmation status of the alteration and/or germline origin was not available for these cases, and the variant's presence in gnomAD precludes the use of PS4. Functional data exist for this variant, but it does not meet the criteria for established assays assessing RUNX1 function (PS3/BS3 not met). In vitro studies have demonstrated that Ser424 is a phosphorylation target of CDK/Cyclin complexes (PMID: 18003885). However, the S424A variant does not appear to impair transactivation, affect interaction with HDAC1, or alter levels of marrow progenitor proliferation compared to the wild type, although collective alterations at S48, S303, and S424 may impact this pathway (PMID: 18003885; PMID: 21059642). The computational predictor REVEL gives a score of 0.284, 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	ℹ	✔	This missense variant has a REVEL score < 0.50 (0.284) and a SpliceAI score ≤ 0.20 (0.00) (BP4).

Not Met criteria codes

PP1	ℹ	✖	Segregation data for this variant has not been reported in literature.
PP2		✖	This rule is not applicable for MM-VCEP.
PP3	ℹ	✖	This missense variant does not have a REVEL score of ≥ 0.88.
PP4		✖	This rule is not applicable for MM-VCEP.
PVS1	ℹ	✖	This variant is not a null variant.
BS2		✖	This rule is not applicable for MM-VCEP
BS1	ℹ	✖	- Completely absent from gnomAD v2 with a mean coverage of at least 20X. - gnomAD (v3): ALL: 0.01999% (29/145066) - SAS: 0.1702% (7/4114) - EAS: 0.09363% (4/4272) - FIN: 0.04223% (4/9472) - AFR: 0.02001% (8/39984) - AMR: 0.01359% (2/14720) - NFE: 0.006069% (4/65908) - gnomAD (v4): ALL: 0.2740% (3159/1152872) - EAS: 1.053% (255/24222) - ASJ: 0.7780% (171/21980) - FIN: 0.6145% (234/38078) - RMG: 0.5760% (247/42882) - MEAS: 0.3823% (18/4708) - NFE: 0.2347% (1956/833514) - AMR: 0.2258% (103/45624) - AFR: 0.1964% (125/63640) - SAS: 0.06464% (50/77354) *Allele balance is skewed in gnomAD v3 and v4 and site quality metric may be lower than other common (variant seems to be in a GC-rich region), pathogenic variants.
BS4	ℹ	✖	Segregation data for this variant has not been reported in literature.

BS3	ℹ	✖	Functional data for this variant is available, but it is not one of the established assays for assessing RUNX1 function. In vitro functional data demonstrated that Ser424 is a phosphorylation target of CDK/Cyclin complexes, and phosphorylation of a series of serine residues increases the transactivation activity of RUNX1. However, S424A does not significantly impair transactivation when compared to WT (PMID: 18003885). Phosphorylation of these serine residues is also expected to reduce the phosphorylation of HDAC1/3, but S424A did not affect the interaction with HDAC1 and did not affect marrow progenitor proliferation (PMID: 21059642). While Ser424 is a phosphorylation residue, it seems that the impact on this pathway is dependent on S48, S303, and S424 collectively.
BP3		✖	This rule is not applicable for MM-VCEP.
BP1		✖	This rule is not applicable for MM-VCEP.
BP2	ℹ	✖	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. Homozygotes are also not reported in gnomAD.
BP5		✖	This rule is not applicable for MM-VCEP.
BP7	ℹ	✖	This variant is not a synonymous or intronic variant.
PS1	ℹ	✖	S424A/S397A will not arise from any other single nucleotide substitution. In addition, there has not yet been a missense change determined to be pathogenic at this amino acid.
PS2		✖	De novo data for this variant has not been reported in literature.
PS3	ℹ	✖	Functional data for this variant is available, but it is not one of the established assays for assessing RUNX1 function. In vitro functional data demonstrated that Ser424 is a phosphorylation target of CDK/Cyclin complexes, and phosphorylation of a series of serine residues increases the transactivation activity of RUNX1. However, S424A does not significantly impair transactivation when compared to WT (PMID: 18003885). Phosphorylation of these serine residues is also expected to reduce the phosphorylation of HDAC1/3, but S424A did not affect the interaction with HDAC1 and did not affect marrow progenitor proliferation (PMID: 21059642). While Ser424 is a phosphorylation residue, it seems that the impact on this pathway is dependent on S48, S303, and S424 collectively.
PS4	ℹ	✖	The variant has been reported in a 32-year-old female with thrombocytopenia and a delayed secretion defect, but germline origin was presumed instead of confirmed by tissue or familial testing (PMID: 32935436). It has also been reported in a Chinese patient with newly-diagnosed AML (PMID: 34234861) and a Chinese infant with AML (PMID: 35814831), but variant allele fraction suggests either somatic origin or artifact (unconfirmed). Finally, the variant has been reported in other patients/tumors without germline/somatic confirmation (PMID: 30239046; PMID: 32359397; PMID: 32963611; PMID: 33242424; PMID: 35342043; PMID: 35626111; PMID: 35988589; PMID: 36761421; PMID: 37072338; PMID: 37142644; PMID: 37160887; PMID: 37661782), except perhaps a family of two brothers (BC at 25 and RCC at 35) and an unaffected parent who underwent WES (PMID: 35625741). Although the reports in patients with hematological conditions is noteworthy, the presence in gnomAD precludes the application of PS4 at any strength level.
BA1	ℹ	✖	- Completely absent from gnomAD v2 with a mean coverage of at least 20X - gnomAD (v3): ALL: 0.01999% (29/145066) - SAS: 0.1702% (7/4114) - EAS: 0.09363% (4/4272) - FIN: 0.04223% (4/9472) - AFR: 0.02001%

(8/39984) - AMR: 0.01359% (2/14720) - NFE: 0.006069% (4/65908) - gnomAD (v4): ALL: 0.2740% (3159/1152872) - EAS: 1.053% (255/24222) - ASJ: 0.7780% (171/21980) - FIN: 0.6145% (234/38078) - RMG: 0.5760% (247/42882) - MEAS: 0.3823% (18/4708) - NFE: 0.2347% (1956/833514) - AMR: 0.2258% (103/45624) - AFR: 0.1964% (125/63640) - SAS: 0.06464% (50/77354) *Allele balance is skewed in gnomAD v3 and v4 and site quality metric may be lower than other common (variant seems to be in a GC-rich region), pathogenic variants.

PM6	ℹ	✖	De novo data for this variant has not been reported in literature.
PM2		✖	- Completely absent from gnomAD v2 with a mean coverage of at least 20X. - gnomAD (v3): ALL: 0.01999% (29/145066) - SAS: 0.1702% (7/4114) - EAS: 0.09363% (4/4272) - FIN: 0.04223% (4/9472) - AFR: 0.02001% (8/39984) - AMR: 0.01359% (2/14720) - NFE: 0.006069% (4/65908) - gnomAD (v4): ALL: 0.2740% (3159/1152872) - EAS: 1.053% (255/24222) - ASJ: 0.7780% (171/21980) - FIN: 0.6145% (234/38078) - RMG: 0.5760% (247/42882) - MEAS: 0.3823% (18/4708) - NFE: 0.2347% (1956/833514) - AMR: 0.2258% (103/45624) - AFR: 0.1964% (125/63640) - SAS: 0.06464% (50/77354) *Allele balance is skewed in gnomAD v3 and v4 and site quality metric may be lower than other common (variant seems to be in a GC-rich region), pathogenic variants.
PM1		✖	This variant is not located at a hotspot (R107, K110, A134, R162, R166, S167, R169, G170, K194, T196, D198, R210, R204) or within residues 89-204.
PM3		✖	This rule is not applicable for MM-VCEP.
PM5	ℹ	✖	There has not yet been a different missense change determined to be pathogenic at this amino acid residue.
PM4	ℹ	✖	This variant is not an in-frame deletion/insertion.

Curation History

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