Variant: NM_001754.4(RUNX1):c.1196G>T (p.Ser399Ile)

Version: 1.0

CA320251372

532658 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: c7f454da-b262-4987-a3b3-f3d8bfd3c4e1
Approved on: 2024-08-12
Published on: 2024-08-12

HGVS expressions

NM_001754.4:c.1196G>T
NM_001754.4(RUNX1):c.1196G>T (p.Ser399Ile)
NC_000021.9:g.34792382C>A
CM000683.2:g.34792382C>A
NC_000021.8:g.36164679C>A
CM000683.1:g.36164679C>A
NC_000021.7:g.35086549C>A
NG_011402.2:g.1197330G>T
ENST00000675419.1:c.1196G>T
ENST00000300305.7:c.1196G>T
ENST00000344691.8:c.1115G>T
ENST00000399240.5:c.923G>T
ENST00000437180.5:c.1196G>T
ENST00000482318.5:c.*786G>T
NM_001001890.2:c.1115G>T
NM_001001890.3:c.1115G>T
NM_001754.5:c.1196G>T

Uncertain Significance

Met criteria codes 1

BP4

Not Met criteria codes 25

PS1 PS2 PS3 PS4 BA1 PP1 PP2 PP3 PP4 PM6 PM2 PM1 PM3 PM5 PM4 PVS1 BS2 BS1 BS4 BS3 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_001754.4(RUNX1):c.1196G>T (p.Ser399Ile) is a missense variant which has a REVEL score < 0.50 (0.116) and SpliceAI does not predict (Δ scores ≤ 0.20) a significant impact on the canonical splice sites or the creation of putative cryptic splice sites (BP4). The variant has been published in a pediatric patient with B-ALL, which was confirmed to be in the germline based on assessment in a remission sample (PMID: 34166225). It was also identified in a male patient with primary myelofibrosis, but the germline assessment was based on a buccal mucosa sample (PMID: 31135094), and in a 58-year-old Greek patient with ovarian cancer who also carried RAD51C c.90del/p.F32Sfs*8 (LOVD: Individual #00021433). However, PS4_supporting cannot be applied because the variant presents more than 2 times in gnomAD (5 heterozygotes in v2 and 1 heterozygote in v3). In summary, the clinical significance of this variant is uncertain. ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy Variant Curation Expert Panel for RUNX1: BP4.

Met criteria codes

BP4	✔	REVEL score = 0.116, 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

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	✖	Expression of the mutant protein was demonstrated in vitro (Fig. S1), and transactivation of the SPI1 promoter in HeLa cells using a luciferase reporter assay was 71.55% of WT (Table S10) (PMID: 34166225).
PS4	✖	The variant has been published in a pediatric patient with B-ALL, which was confirmed to be in the germline based on assessment in a remission sample (PMID: 34166225). It was also identified in a male patient with primary myelofibrosis who also had germline JAK2 N1108S and somatic ASXL1 and ZRSR2 alterations, but this assessment was based on buccal mucosa sample (PMID: 31135094). Finally, the variant was identified in a 58yo Greek patient with ovarian cancer who also carried RAD51C c.90del/p.F32Sfs*8 (LOVD:Individual #00021433).
BA1	✖	gnomAD (v2): ALL: 0.002893% (5/172810) - AMR: 0.01154% (3/25986) - NFE: 0.001420% (1/70420) - OTH: 0.02134% (1/4686) gnomAD (v3): ALL: 0.0006585 (1/151858) - AMR: 0.006545% (1/15278)
PP1	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
PP2	✖	Not applicable
PP3	✖	REVEL score = 0.116, 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	✖	

No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.

PM2		✖	gnomAD (v2): ALL: 0.002893% (5/172810) - AMR: 0.01154% (3/25986) - NFE: 0.001420% (1/70420) - OTH: 0.02134% (1/4686) gnomAD (v3): ALL: 0.0006585 (1/151858) - AMR: 0.006545% (1/15278)
PM1		✖	Not located at a hotspot (R107, K110, A134, R162, R166, S167, R169, G170, K194, T196, D198, R210, R204) or within residues 89-204.
PM3		✖	Not applicable
PM5	ℹ	✖	S399N/S372N has been reported the most in Mastermind, but data is likely insufficient for LP/P classification.
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	Not applicable
BS1	ℹ	✖	gnomAD (v2): ALL: 0.002893% (5/172810) - AMR: 0.01154% (3/25986) - NFE: 0.001420% (1/70420) - OTH: 0.02134% (1/4686) gnomAD (v3): ALL: 0.0006585 (1/151858) - AMR: 0.006545% (1/15278)
BS4	ℹ	✖	No relevant cases found in literature search, including LOVD, HGMD, ClinVar, COSMIC, Mastermind, and Google/Google Scholar searches.
BS3	ℹ	✖	Expression of the mutant protein was demonstrated in vitro (Fig. S1), and transactivation of the SPI1 promoter in HeLa cells using a luciferase reporter assay was 71.55% of WT (Table S10) (PMID: 34166225).
BP5		✖	Not applicable
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 code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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