Variant: NM_001754.5(RUNX1):c.812G>A (p.Arg271Lys)

Version: 1.0

CA10014290

699735 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3838deae-bde1-4eb8-8c28-ff7714f3e455
Approved on: 2024-06-24
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HGVS expressions

NM_001754.5:c.812G>A
NM_001754.5(RUNX1):c.812G>A (p.Arg271Lys)
NC_000021.9:g.34799456C>T
CM000683.2:g.34799456C>T
NC_000021.8:g.36171753C>T
CM000683.1:g.36171753C>T
NC_000021.7:g.35093623C>T
NG_011402.2:g.1190256G>A
ENST00000675419.1:c.812G>A
ENST00000300305.7:c.812G>A
ENST00000344691.8:c.731G>A
ENST00000399240.5:c.539G>A
ENST00000437180.5:c.812G>A
ENST00000482318.5:c.*402G>A
NM_001001890.2:c.731G>A
NM_001754.4:c.812G>A
NM_001001890.3:c.731G>A

Benign

Met criteria codes 2

BP4 BA1

Not Met criteria codes 24

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

Evidence Links 0

Expert Panel

Myeloid Malignancy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Myeloid Malignancy VCEP

This missense variant has been published in Taiwanese patients with CEBPA double-mutated, cytogenetically normal-AML (PMID: 29773598), pediatric T-ALL (PMID: 30280491), and ovarian cancer (PMID: 31761620), although germline origin was unknown for these cases. However, the variant has an MAF of 0.1854% (37/19952 alleles) in the East Asian subpopulation of the gnomAD cohort, which is ≥ 0.0015 (0.15%) (BA1). It also has a REVEL score <0.50 (0.326) 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). In summary, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy Variant Curation Expert Panel for RUNX1: BA1, BP4.

Met criteria codes

BP4	✔	REVEL score = 0.326, which is less than the v2 threshold of 0.50. SpliceAI doesn't predict any significant splicing impact (Δ scores ≤ 0.20).
BA1	✔	gnomAD (v2): ALL: 0.01308% (37/282814) - EAS: 0.1854% (37/19952) gnomAD (v3): ALL: 0.003287% (5/152106) - EAS: 0.09634% (5/5190)

Not Met criteria codes

BS2	✖	Not applicable
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	gnomAD (v2): ALL: 0.01308% (37/282814) - EAS: 0.1854% (37/19952) gnomAD (v3): ALL: 0.003287% (5/152106) - EAS: 0.09634% (5/5190)
BS4	✖	Family studies were not found in the literature (LOVD, HGMD, ClinVar, COSMIC, Google/Google Scholar, Mastermind).
BS3	✖	Functional studies were not found in the literature (LOVD, HGMD, ClinVar, COSMIC, Google/Google Scholar, Mastermind).
BP3	✖	Not applicable
BP1	✖	Not applicable
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	Not applicable
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS2	✖	Germline confirmed/de novo cases were not found in the literature (LOVD, HGMD, ClinVar, COSMIC, Google/Google Scholar, Mastermind).
PS3	✖	Functional studies were not found in the literature (LOVD, HGMD, ClinVar, COSMIC, Google/Google Scholar, Mastermind).
PS4	✖	The variant has been published in patients from Taiwan: CEBPAdm-mutated CN-AML of a 41yo female (PMID: 29773598), a pediatric T-ALL (PMID: 30280491), and an ovarian tumor at VAF=29% (PMID: 31761620). However, germline origin is unknown for these cases.
PP1	✖	Family studies were not found in the literature (LOVD, HGMD, ClinVar, COSMIC, Google/Google Scholar, Mastermind).
PP2	✖	Not applicable
PP3	✖	REVEL score = 0.326, 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
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	✖	R271/R244 variants have not been reported in COSMIC or Mastermind.
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	Germline confirmed/de novo cases were not found in the literature (LOVD, HGMD, ClinVar, COSMIC, Google/Google Scholar, Mastermind).
PM2	✖	gnomAD (v2): ALL: 0.01308% (37/282814) - EAS: 0.1854% (37/19952) gnomAD (v3): ALL: 0.003287% (5/152106) - EAS: 0.09634% (5/5190)

Curation History

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