Variant: NM_001754.4(RUNX1):c.205G>C (p.Gly69Arg)

CA10014569

463990 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8ea17be0-3ed0-4d8a-b328-0a6493331461
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HGVS expressions

NM_001754.4:c.205G>C
NM_001754.4(RUNX1):c.205G>C (p.Gly69Arg)
NM_001001890.2:c.124G>C
NM_001122607.1:c.124G>C
NM_001001890.3:c.124G>C
NM_001122607.2:c.124G>C
NM_001754.5:c.205G>C
ENST00000300305.7:c.205G>C
ENST00000344691.8:c.124G>C
ENST00000358356.9:c.124G>C
ENST00000399237.6:c.169G>C
ENST00000399240.5:c.124G>C
ENST00000437180.5:c.205G>C
ENST00000455571.5:c.166G>C
ENST00000482318.5:c.59-6276G>C
NC_000021.9:g.34886989C>G
CM000683.2:g.34886989C>G
NC_000021.8:g.36259286C>G
CM000683.1:g.36259286C>G
NC_000021.7:g.35181156C>G
NG_011402.2:g.1102723G>C

Benign

Met criteria codes 2

BS1 BS3

Not Met criteria codes 16

BA1 BS4 BP7 BP4 BP2 PS1 PS3 PS4 PVS1 PP3 PP1 PM5 PM4 PM1 PM2 PM6

Evidence Links 2

Expert Panel

Myeloid Malignancy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Myeloid Malignancy VCEP

The NM_001754.4:c.205G>C variant that results in a Gly69Arg missense change has an MAF of 0.0003133 (0.03%, 6/19148 alleles) in the East Asian subpopulation of the gnomAD v2.1.1 cohort, which is between 0.00015 (0.015%) and 0.0015 (0.15%) (BS1). Transactivation assays demonstrate normal transactivation as wild-type and normal DNA binding (BS3; PMIDs: 23817177 & 12393679). The variant has not been reported in the germ line of patients with familial platelet disorder with predisposition to hematologic malignancies in the literature, to the best of our knowledge. In summary, this variant meets criteria to be classified as benign. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: BS1, BS3.

Met criteria codes

BS1	✔	The variant is reported at a frequency of 0.0003133 (6/19148 East Asian alleles) in gnomAD v2.1.1 and at a frequency of 0.0009572 (3/3134 East Asian alleles) in gnomAD v3. The gnomAD v2 frequency meets criteria for BS1; threshold: >0.00015
BS3	✔	Evidence from PMID: 23817177 and PMID: 12393679 meet criteria for BS3. Luciferase assay in HeLa cells demonstrated that the variant induced promoter activity similar to wild-type (Fig 3A) and DNA-binding ability in EMSA on nuclear extracts from COS-7 cells was similar or enhanced compared to wild-type (Fig 2A). Experiment included Arg204Gln (pathogenic control). PubMed:12393679 Luciferase reporter assay in U937 cells showed normal transactivation (Figure 4) and EMSA in COS7 cells showed normal DNA binding (Figure 2). Experiment included Arg201Gln (pathogenic control). PubMed:23817177

Not Met criteria codes

BA1	✖	Meets BS1
BS4	✖	No data currently available
BP7	✖	N/A
BP4	✖	The variant has a REVEL score of 0.559; threshold: <0.15
BP2	✖	N/A
PS1	✖	No data currently available
PS3	✖	Meets BS3
PS4	✖	The variant has not been reported in the germ line of patients with familial platelet disorder with predisposition to hematologic malignancies in the literature, to the best of our knowledge. It has been reported as a somatic variant, with no clinical significance. (PMID: 12393679 reports the variant in two patients with radiation-associated and therapy-related MDS/AML).
PVS1	✖	N/A

PP3		✖	The variant has a REVEL score of 0.559; threshold: >0.75
PP1		✖	No data currently available
PM5		✖	No data currently available
PM4		✖	N/A
PM1		✖	N/A
PM2		✖	Meets BS1
PM6		✖	No data currently available

Curation History

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene

No matching records found