The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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

Version: 1.0

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
Approved on: 2021-01-11
Published on: 2021-01-11

HGVS expressions

NM_001754.4:c.205G>C
NM_001754.4(RUNX1):c.205G>C (p.Gly69Arg)
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
ENST00000675419.1: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
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

Benign

Met criteria codes 2

BS1 BS3

Not Met criteria codes 24

BA1 BS2 BS4 BP4 BP3 BP1 BP2 PVS1 BP5 BP7 PS1 PS2 PS3 PS4 PP1 PP2 PP3 PP4 PM1 PM3 PM5 PM4 PM6 PM2

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
BS2	✖	MM-VCEP deemed N/A for RUNX1
BS4	✖	No data currently available
BP4	✖	The variant has a REVEL score of 0.559; threshold: <0.15
BP3	✖	MM-VCEP deemed N/A for RUNX1
BP1	✖	MM-VCEP deemed N/A for RUNX1
BP2	✖	N/A
PVS1	✖	N/A
BP5	✖	MM-VCEP deemed N/A for RUNX1

BP7	✖	N/A
PS1	✖	No data currently available
PS2	✖	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).
PP1	✖	No data currently available
PP2	✖	MM-VCEP deemed N/A for RUNX1
PP3	✖	The variant has a REVEL score of 0.559; threshold: >0.75
PP4	✖	MM-VCEP deemed N/A for RUNX1
PM1	✖	N/A
PM3	✖	MM-VCEP deemed N/A for RUNX1
PM5	✖	No data currently available
PM4	✖	N/A
PM6	✖	No data currently available
PM2	✖	Meets BS1

Curation History

Showing 1 to 1 of 1 rows