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# *Variant: NM_001754.5(RUNX1):c.496C>T (p.Arg166Ter)*

Version: 1.0

*CA410202490*

*1459069 (ClinVar)*

**Gene**: RUNX1 (HGNC:861)
**Condition**: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 8a2da505-9427-4852-82be-47e489d4a0f4
**Approved on**: 2022/4/25
**Published on**: 2022/7/5

## *HGVS expressions*

**NM_001754.5(RUNX1):c.496C>T (p.Arg166Ter)**
**NM_001754.5:c.496C>T**
NC_000021.9:g.34880569G>A
CM000683.2:g.34880569G>A
NC_000021.8:g.36252866G>A
CM000683.1:g.36252866G>A
NC_000021.7:g.35174736G>A
NG_011402.2:g.1109143C>T
ENST00000675419.1:c.496C>T
ENST00000300305.7:c.496C>T
ENST00000344691.8:c.415C>T
ENST00000358356.9:c.415C>T
ENST00000399237.6:c.460C>T
ENST00000399240.5:c.415C>T
ENST00000437180.5:c.496C>T
ENST00000482318.5:c.*86C>T
NM_001001890.2:c.415C>T
NM_001122607.1:c.415C>T
NM_001754.4:c.496C>T
NM_001001890.3:c.415C>T
NM_001122607.2:c.415C>T

**Pathogenic**

**Met criteria codes** 3

PVS1 PM2_Supporting PS4_Supporting

**Not Met criteria codes** 23

PS1 PS2 PS3 PP1 PP2 PP3 PP4 PM6 PM1 PM3 PM5 PM4 BA1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2

Evidence Links 1

Expert Panel

Myeloid Malignancy VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Myeloid Malignancy VCEP***

**NM_001754.5(RUNX1):c.496C>T (p.Arg166Ter) is a nonsense variant that is predicted to undergo NMD (PVS1, SNV Tree). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_ Supporting; PMID: 27210295). In summary, this variant meets the criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PVS1, PM2_supporting, PS4_supporting.**

**Met criteria codes**

| | | |
|---|---|---|
| **PVS1** | ✔ | NM_001754.5(RUNX1):c.496C>T (p.Arg166Ter) is a nonsense variant that is predicted to undergo NMD (PVS1, SNV Tree) |
| **PM2_Supporting** | ✔ | This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). |
| **PS4_Supporting** | ✔ | This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_ Supporting; PMID: 27210295) |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PS1** | ✖ | Not a missense variant |
| **PS2** | ✖ | This variant has not been seen in de novo |
| **PS3** | ✖ | : Transactivation assays demonstrating enhanced transactivation (>115% of wt) (PS3_Supporting; PMID: 33692461) Cannot be applied because meet PVS1<br>R139* shows Transactivation assays demonstrating altered transactivation (<20% of wt, and/or reduced to levels similar to well-established pathogenic variants such as R201Q or R166Q) in luciferase assay PubMed:33692461 |
| **PP1** | ✖ | This variant seems to co-segregate with disease in multiple affected family members, with three or four (X) meioses observed in one family/across X families (PP1; PMID: 27210295) however cannot be confirmed. |
| **PP2** | ✖ | This rule is not applicable for MM-VCEP |
| **PP3** | ✖ | Not a missense, synonymous, or intronic variant |
| **PP4** | ✖ | This rule is not applicable for MM-VCEP |
| **PM6** | ✖ | This variant has not been seen in de novo |

| | | | |
|---|---|---|---|
| **PM1** | | ✖ | Not a missense variant |
| **PM3** | | ✖ | This rule is not applicable for MM-VCEP |
| **PM5** | ℹ | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM4** | ℹ | ✖ | Not an in-frame deletion/insertion |
| **BA1** | ℹ | ✖ | This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). |
| **BS2** | | ✖ | This rule is not applicable for MM-VCEP |
| **BS1** | ℹ | ✖ | This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). |
| **BS4** | ℹ | ✖ | This variant seems to co-segregate with disease in multiple affected family members, with three or four (X) meioses observed in one family/across X families (PP1; PMID: 27210295) however cannot be confirmed. |
| **BS3** | ℹ | ✖ | : Transactivation assays demonstrating enhanced transactivation (>115% of wt) (PS3_Supporting; PMID: 33692461) Cannot be applied because meets PVS1<br><br>R139* shows Transactivation assays demonstrating altered transactivation (<20% of wt, and/or reduced to levels similar to well-established pathogenic variants such as R201Q or R166Q) in luciferase assay PubMed:33692461 |
| **BP5** | | ✖ | This rule is not applicable for MM-VCEP |
| **BP7** | ℹ | ✖ | Not a synonymous or intronic variant |
| **BP4** | ℹ | ✖ | Not a missense, synonymous, or intronic variant |
| **BP3** | | ✖ | This rule is not applicable for MM-VCEP |
| **BP1** | | ✖ | This rule is not applicable for MM-VCEP |
| **BP2** | ℹ | ✖ | Not seem in homozygotes in gnomAD v2.1.1 and v3.1.2 |

Curation History

Showing 1 to 1 of 1 rows

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