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# *Variant: NM_001754.5(RUNX1):c.497G>A (p.Arg166Gln)*

Version: 1.2

*CA16616941*

*417961 (ClinVar)*

**Gene**: RUNX1 (HGNC:861)
**Condition**: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** ba8c0c9c-028c-473b-9259-a8316db5b16d
**Approved on**: 2026/5/27
**Published on**: 2026/5/27

## *HGVS expressions*

**NM_001754.5:c.497G>A**
**NM_001754.5(RUNX1):c.497G>A (p.Arg166Gln)**
NC_000021.9:g.34880568C>T
CM000683.2:g.34880568C>T
NC_000021.8:g.36252865C>T
CM000683.1:g.36252865C>T
NC_000021.7:g.35174735C>T
NG_011402.2:g.1109144G>A
ENST00000675419.1:c.497G>A
ENST00000300305.7:c.497G>A
ENST00000344691.8:c.416G>A
ENST00000358356.9:c.416G>A
ENST00000399237.6:c.461G>A
ENST00000399240.5:c.416G>A
ENST00000437180.5:c.497G>A
ENST00000482318.5:c.*87G>A
NM_001001890.2:c.416G>A
NM_001122607.1:c.416G>A
NM_001754.4:c.497G>A
NM_001001890.3:c.416G>A
NM_001122607.2:c.416G>A

**Pathogenic**

**Met criteria codes** 7

PS4_Moderate PM6_Supporting PM1_Strong PS3 PM2_Supporting PP1 PP3

**Not Met criteria codes** 19

PM3 PM5 PM4 BA1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PVS1 PP2 PP4

Evidence Links 6

## Expert Panel

Myeloid Malignancy VCEP

## Criteria Specification Information

- **Criteria Specification:** *ClinGen Myeloid Malignancy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RUNX1 Version 3.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Myeloid Malignancy VCEP***

**NM_001754.5(RUNX1):c.497G>A (p.Arg166Gln) is a missense variant which affects one of the hotspot residues (R166) within the RHD (PM1_Strong). Transactivation assays demonstrate altered transactivation (<20% of wt) and data from secondary assays demonstrate altered DNA binding, CBFβ binding, and sub-cellular localization (PS3; PMID: 11830488, 25840971, 23848403). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting) and has a REVEL score of >0.75 (0.96) (PP3). This variant has been reported in three probands meeting at least one of the RUNX1-phenotypic criteria (PS4_Moderate; PMID: 10508512, 28960434, 26175287) and was found to co-segregate with disease in multiple affected family members, with three meioses observed across one family (PP1; PMID: 10508512). This variant was reported in two unrelated probands meeting at least one of the RUNX1-phenotypic criteria with assumed de novo occurrence (without confirmation of maternity and paternity) (PM6_ Supporting; PMID: 8960434, 26175287). In summary, this variant meets criteria to be classified as pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1_Strong, PS3, PM2_Supporting, PP3, PS4_Moderate, PP1, PM6_Supporting.**

**Met criteria codes**

**PS4_Moderate** ✔

This variant has been reported in 3 probands meeting at least one of RUNX1 phenotype criteria (PS4_moderate; PMID: 10508512, 28960434, 26175287).

Reported in patient 5 who has onset-at-birth thrombocytopenia with small or normal-sized platelets and without family history. PubMed:26175287
Reported in individual II-2 in pedigree 6 with FPD/AML (Familial platelet disorder with predisposition to acute myeloid leukemia). This individual had preleukemia with trisomy 8. The variant This variant co-segregates with disease in this family (see PP1). PubMed:10508512
Reported in the patient 182 who has suspected inherited thrombocytopenia. PubMed:28960434

**PM6_Supporting** ✔

There are two probands meeting at least one of the RUNX1- phenotypic criteria with assumed de novo occurrence (without confirmation of maternity and paternity) (PM6_ Supporting; PMID: 28960434, 26175287).

Reported as a de novo change in patient 5 who has onset-at-birth thrombocytopenia with small or normal-sized platelets and without family history. None of the parents carried this variant. PubMed:26175287
Reported as a de novo variant in the patient 182 who has suspected inherited thrombocytopenia through proband-only exome sequencing and parental studies. PubMed:28960434

**PM1_Strong** ✔

This variant affects at least one of the following hotspot residues within the RHD: (R166)(PM1_strong).

**PS3** ✔

Transactivation assays demonstrating altered transactivation (<20% of WT) and data from a secondary assays demonstrating altered DNA binding, CBFβ binding, and sub-cellular localization (PS3; PMID: 11830488, 25840971, 23848403).

Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered CBFβ binding and sub-cellular localization. PubMed:11830488
Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered DNA binding and CBFβ binding. PubMed:25840971
Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered CBFβ binding and sub-cellular localization. PubMed:23848403

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|---|---|---|
| **PM2_Supporting** | ✔ | The variant is absent from all population databases. |
| **PP1** | ✔ | This variant was found to co-segregate with disease in multiple affected family members, with four meioses observed in one family (PP1; PMID: 10508512).<br><br>This variant was found to co-segregate with the FPD/AML (Familial platelet disorder with predisposition to acute myeloid leukemia) trait in four affected family members in pedigree 6. PubMed:10508512 |
| **PP3** | ✔ | REVEL: 0.962 >0.75 |

**Not Met criteria codes**

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|---|---|---|
| **PM3** | ✖ | Not applicable. |
| **PM5** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PM4** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BA1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS2** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS4** | ✖ | No evidence<br><br>This variant was found to co-segregate with the FPD/AML (Familial platelet disorder with predisposition to acute myeloid leukemia) trait in four affected family members in pedigree 6. PubMed:10508512 |
| **BS3** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BP4** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BP3** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BP1** | ✖ | |

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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|---|---|---|
| **BP2** | ✖ | No evidence |
| **BP5** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **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** | ✖ | Reported as de novo but without confirmation of maternity/paternity.<br>Reported as a de novo change in patient 5 who has onset-at-birth thrombocytopenia with small or normal-sized platelets and without family history. None of the parents carried this variant. PubMed:26175287<br>Reported as a de novo variant in the patient 182 who has suspected inherited thrombocytopenia through proband-only exome sequencing and parental studies. PubMed:28960434 |
| **PVS1** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PP2** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PP4** | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

Curation History

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