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Variant: NM_001754.5(RUNX1):c.592G>T (p.Asp198Tyr)

Version: 2.0

CA410207975

2665098 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 0bb54213-b944-4359-9c06-3c5e6d93feef
Approved on: 2026/4/29
Published on: 2026/4/29

HGVS expressions

NM_001754.5(RUNX1):c.592G>T (p.Asp198Tyr)
NM_001754.5:c.592G>T
NC_000021.9:g.34859495C>A
CM000683.2:g.34859495C>A
NC_000021.8:g.36231792C>A
CM000683.1:g.36231792C>A
NC_000021.7:g.35153662C>A
NG_011402.2:g.1130217G>T
ENST00000675419.1:c.592G>T
ENST00000300305.7:c.592G>T
ENST00000344691.8:c.511G>T
ENST00000358356.9:c.511G>T
ENST00000399237.6:c.556G>T
ENST00000399240.5:c.511G>T
ENST00000437180.5:c.592G>T
ENST00000467577.1:n.84G>T
ENST00000482318.5:c.*182G>T
NM_001001890.2:c.511G>T
NM_001122607.1:c.511G>T
NM_001754.4:c.592G>T
NM_001001890.3:c.511G>T
NM_001122607.2:c.511G>T

Pathogenic

Met criteria codes 6

PM1_Strong PS3_Moderate PP1 PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 20

PVS1 PM6 PM3 PM5 PM4 BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PP2 PP4

Evidence Links 2

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.592G>T (p.Asp198Tyr) is a missense variant which affects on of the hotspot residues (D198) in the RHD (PM1_strong) and is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). Yeast assays demonstrated decreased DNA binding, CBFβ binding, and promoter activation (PMID: 17290219, 23848403)(PS3_moderate), and a REVEL score ≥ 0.88 (0.964) supports a deleterious effect (PP3). This variant has been reported in a proband meeting RUNX1 phenotypic criteria and was found to co-segregate with disease in multiple affected family members (PMID: 11675361) (PS4_supporting, PP1). 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, PM2_supporting, PS3_moderate, PP3, PS4_supporting, PP1.

Met criteria codes

PM1_Strong	✔	This variant affects the following hotspot residue within the RHD: D198 (PM1_strong).
PS3_Moderate	✔	Yeast assays showed significant decreased DNA binding, CBFbeta binding and promoter activation indicating that this variant impacts protein function (PMIDs: 17290219, 23848403) (PS3_moderate). Yeast assays showed significant decreased DNA binding, CBFbeta binding and promoter activation indicating that this variant impacts protein function (PMIDs). PubMed:17290219 Yeast assays showed significant decreased DNA binding, CBFbeta binding and promoter activation indicating that this variant impacts protein function (PMIDs). PubMed:23848403
PP1	✔	This variant has been reported to co-segregate with disease in 3 affected individuals in a family meeting RUNX-1 phenotypic criteria (FPD and/or AML) (PMID 11675361) (PP1_supporting).
PP3	✔	This missense variant has a REVEL score ≥ 0.88 (0.964) (PP3).
PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 in gnomAD v2.1.1 and v3.1.2 (PM2_supporting).
PS4_Supporting	✔	This variant has been reported in a proband meeting RUNX-1 phenotypic criteria (FPD and/or AML) (PMID 11675361) (PS4_moderate).

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	LP *** 2019 > should be updated with specifications?
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	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
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	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		✖	This rule is not applicable to the MMVCEP.
BP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP2	✖	This rule is not applicable to the MMVCEP.
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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