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Variant: NM_001754.5(RUNX1):c.596G>A (p.Gly199Glu)

Version: 1.2

CA410207966

869210 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: de750d9a-56cc-4163-b7de-f2837e11ad9b
Approved on: Thu, 15 Oct 2026 00:00:00 +0000
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HGVS expressions

NM_001754.5(RUNX1):c.596G>A (p.Gly199Glu)
NM_001754.5:c.596G>A
NC_000021.9:g.34859491C>T
CM000683.2:g.34859491C>T
NC_000021.8:g.36231788C>T
CM000683.1:g.36231788C>T
NC_000021.7:g.35153658C>T
NG_011402.2:g.1130221G>A
ENST00000675419.1:c.596G>A
ENST00000300305.7:c.596G>A
ENST00000344691.8:c.515G>A
ENST00000358356.9:c.515G>A
ENST00000399237.6:c.560G>A
ENST00000399240.5:c.515G>A
ENST00000437180.5:c.596G>A
ENST00000467577.1:n.88G>A
ENST00000482318.5:c.*186G>A
NM_001001890.2:c.515G>A
NM_001122607.1:c.515G>A
NM_001754.4:c.596G>A
NM_001001890.3:c.515G>A
NM_001122607.2:c.515G>A

Likely Pathogenic

Met criteria codes 5

PM1_Supporting PP1 PP3 PM2_Supporting PS4_Moderate

Not Met criteria codes 21

PP2 PP4 PM3 PM5 BA1 PM4 PM6 BS2 BS1 BS4 BS3 PS1 PS2 PS3 BP4 BP3 BP1 BP2 PVS1 BP5 BP7

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*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.4:c.596G>A (p.Gly199Glu) is a missense variant which affects one of the amino acid residues (Gly199) within the RHD (amino acids 89-204; PM1_Supporting). This variant has a REVEL score ≥ 0.88 (0.96) (PP3) and is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting). This variant has been reported in two probands meeting at least one of the RUNX1-phenotypic criteria (PS4_Moderate; PMID: 26884589, 25159113, 24732596) and was found to co-segregate with disease in three observed meioses across two families (PP1; PMID: 26884589, 25159113, 24732596). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PM1_Supporting, PP3, PM2_Supporting, PS4_Moderate, PP1.

Met criteria codes

PM1_Supporting	✔	This variant affects one of the other residues (AA 89-204) within the RHD (PM1_Supporting).
PP1	✔	2 segregations observed in the family described in PMIDs: 26884589, 25159113, 24732596. 1 segregation seen in an additional family (from internal laboratory data). Together, 3 segregation across 2 families meet criteria fro PP1. 2 family members with thrombocytopenia in addition to the proband (2 segregations) in pedigree 57. In addition, Yoshimi et al, 2014, PMID: 25159113, report detection of another missense variant, p.Asp234Gly, in CDC25C in one of the affected individuals from this family. This Family 57 is likely the same as Pedigree 1 in Sakurai, 2014 - PMID: 24732596. All three reports are on Japanese families with FPD/AML. PubMed:26884589
PP3	✔	This missense variant has a REVEL score ≥ 0.88 (0.956) (PP3).
PM2_Supporting	✔	This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_Supporting).
PS4_Moderate	✔	One proband from PMIDs: 26884589, 25159113, 24732596 and one proband from internal laboratory data meet criteria for PS4_Moderate. One proband 51yo (from family 57) with thrombocytopenia and no other bleeding symptoms, diagnosed with FPD/AML. PubMed:26884589

Not Met criteria codes

PP2	✖	This rule is not applicable for MM-VCEP.
PP4	✖	This rule is not applicable for MM-VCEP.
PM3	✖	This rule is not applicable for MM-VCEP.
PM5	✖	There has not yet been a different missense change determined to be pathogenic at this amino acid residue.

BA1	ℹ	✖	This variant does not have a MAF ≥ 0.0015 (0.15%) in any general continental population dataset.
PM4	ℹ	✖	This variant is not an in-frame deletion/insertion.
PM6	ℹ	✖	De novo data for this variant has not been reported in literature.
BS2		✖	This rule is not applicable for MM-VCEP.
BS1	ℹ	✖	This variant does not have a MAF between 0.00015 (0.015%) and 0.0015 (0.15%) in any general continental dataset.
BS4	ℹ	✖	Segregation was not found to be absent in two or more informative meiosis. 2 family members with thrombocytopenia in addition to the proband (2 segregations) in pedigree 57. In addition, Yoshimi et al, 2014, PMID: 25159113, report detection of another missense variant, p.Asp234Gly, in CDC25C in one of the affected individuals from this family. This Family 57 is likely the same as Pedigree 1 in Sakurai, 2014 - PMID: 24732596. All three reports are on Japanese families with FPD/AML. PubMed:26884589
BS3	ℹ	✖	This variant has not been featured in in vitro or in vivo functional studies that show no damaging effect on protein function or splicing. Patient-derived T-cells infected by Sendai viruses to generate iPSCs with the Gly199Glu mutation. Hematopoietic differentiation was induced and analyzed for emergence of hematopoietic progenitors, which was found to be impaired (40-60% of WT for CD34+ and 20-40% for CD45+), but early erythroid-MgK progenitors were not affected. CD34+ cells subjected to colony-forming assays showed significantly reduced GM/E/mix CFCs. PubMed:24732596
PS1	ℹ	✖	There has not yet been a missense change determined to be pathogenic at this amino acid residue.
PS2		✖	De novo data for this variant has not been reported in literature.
PS3	ℹ	✖	Data from PMID: 24732596 shows reduced colony forming potential of CD34+ hematopoietic progenitors of patient-derived iPSCs. However, this evidence does not meet criteria for PS3_Moderate: ≥ 2 secondary assays demonstrating altered function. Patient-derived T-cells infected by Sendai viruses to generate iPSCs with the Gly199Glu mutation. Hematopoietic differentiation was induced and analyzed for emergence of hematopoietic progenitors, which was found to be impaired (40-60% of WT for CD34+ and 20-40% for CD45+), but early erythroid-MgK progenitors were not affected. CD34+ cells subjected to colony-forming assays showed significantly reduced GM/E/mix CFCs. PubMed:24732596
BP4	ℹ	✖	This missense variant does not have a REVEL score < 0.50.
BP3		✖	This rule is not applicable for MM-VCEP.
BP1		✖	This rule is not applicable for MM-VCEP.

BP2		✖	This variant has not been observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.
PVS1		✖	This variant is not a null variant.
BP5		✖	This rule is not applicable for MM-VCEP.
BP7		✖	This variant is not a synonymous or intronic variant.

Curation History

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