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Variant: NM_001754.5(RUNX1):c.601dup (p.Arg201fs)

Version: 1.0

CA913189266

1073884 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 808f09c3-3f62-4523-b5b4-ede068a28f23
Approved on: 2023/12/9
Published on: 2023/12/9

HGVS expressions

NM_001754.5(RUNX1):c.601dup (p.Arg201fs)
NM_001754.5:c.601dup
NC_000021.9:g.34859489dup
CM000683.2:g.34859489dup
NC_000021.8:g.36231786dup
CM000683.1:g.36231786dup
NC_000021.7:g.35153656dup
NG_011402.2:g.1130226dup
ENST00000675419.1:c.601dup
ENST00000300305.7:c.601dup
ENST00000344691.8:c.520dup
ENST00000358356.9:c.520dup
ENST00000399237.6:c.565dup
ENST00000399240.5:c.520dup
ENST00000437180.5:c.601dup
ENST00000467577.1:n.93dup
ENST00000482318.5:c.*191dup
NM_001001890.2:c.520dup
NM_001122607.1:c.520dup
NM_001754.4:c.601dup
NM_001001890.3:c.520dup
NM_001122607.2:c.520dup

Pathogenic

Met criteria codes 4

PVS1 PM2_Supporting PS4_Supporting PM5_Supporting

Not Met criteria codes 22

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

Evidence Links 0

Expert Panel

Myeloid Malignancy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Myeloid Malignancy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Myeloid Malignancy VCEP

NM_001754.5(RUNX1):c.601dup (p.Arg201ProfsTer12) is a frameshift variant. The transcript product is predicted to undergo NMD (PVS1). 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). This variant has been reported in 1 proband with family history meeting RUNX-1 phenotypic criteria (thrombocytopenia) (PMID 26175287) (PS4_supporting). This variant was also reported in Clinvar in 2021 by Invitae but the affected status of the proband is unknown (Variation ID 1073884). There are 25 nonsense/frameshift variants classified as pathogenic by the MM-VCEP in exons 3-7 (two per exon) without use of PM5_Supporting (PMID: 35764482) (PM5_supporting). In summary, the clinical significance of this variant is pathogenic. ACMG/AMP criteria applied, as specified by the Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PVS1, PS4_supporting, PM2_supporting, PM5_supporting.

Met criteria codes

PVS1	✔	The transcript product of this frameshift variant is predicted to undergo NMD.
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 1 proband with family history meeting RUNX-1 phenotypic criteria (thrombocytopenia)](PS4_Supporting]; PMID 26175287. This variant was also reported in Clinvar in 2021 by Invitae but the affected status of the proband is unknown (Variation ID 1073884).
PM5_Supporting	✔	There are 25 nonsense/frameshift variants classified as pathogenic by the MM-VCEP in exons 3-7 (two per exon) without use of PM5_Supporting (PMID: 35764482). This frameshift variant is downstream c.98.

Not Met criteria codes

PM1	✖	This variant is not a missense.
PM3	✖	This rule is not applicable for MM-VCEP.
PM4	✖	This variant is a frameshift.
PM6	✖	There is no proof of testing of other affected family members (PMID 26175287).
BS2	✖	This rule is not applicable to the MMVCEP.
BS1	✖	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).
BS4	✖	There is no proof of testing of other affected family members (PMID 26175287).

BS3	ℹ	✖	To our knowledge, this synonymous variant was not evaluated in transactivation assays. However, p.(Arg201*) was used in Decker et al functional study as a positive pathogenic control has been shown to be damaging.
BP5		✖	This rule is not applicable to the MMVCEP
BP7	ℹ	✖	This variant is a loss-of-function variant.
BP4	ℹ	✖	This variant is a loss-of-function variant.
BP3		✖	This variant is a frameshift.
BP1		✖	This rule is not applicable to the MMVCEP.
BP2	ℹ	✖	No information found in the literature.
BA1	ℹ	✖	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).
PS1	ℹ	✖	This variant is a loss-of-function variant.
PS2		✖	There is no proof of testing of other affected family members (PMID 26175287).
PS3	ℹ	✖	To our knowledge, this synonymous variant was not evaluated in transactivation assays. However, p.(Arg201*) was used in Decker et al functional study as a positive pathogenic control has been shown to be damaging.
PP1	ℹ	✖	There is no proof of testing of other affected family members (PMID 26175287).
PP2		✖	This variant is a loss-of-function variant.
PP3	ℹ	✖	This variant is a loss-of-function variant.
PP4		✖	This rule is not applicable to the MMVCEP.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001754.5(RUNX1):c.601dup (p.Arg...)	Pathogenic	Hereditary Thrombocytopenia And Hematologic Cancer Predisposition Syndrome	2023-12-09	1.0	ClinGen Myeloid Malignancy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2	RUNX1

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