Variant: NM_001754.4:c.315C>A

Version: 1.2

CA410203511

666274 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: f6a20713-2a4b-4e08-91db-86f46749c256
Approved on: 2024-09-10
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HGVS expressions

NM_001754.4:c.315C>A
NC_000021.9:g.34886879G>T
CM000683.2:g.34886879G>T
NC_000021.8:g.36259176G>T
CM000683.1:g.36259176G>T
NC_000021.7:g.35181046G>T
NG_011402.2:g.1102833C>A
ENST00000675419.1:c.315C>A
ENST00000300305.7:c.315C>A
ENST00000344691.8:c.234C>A
ENST00000358356.9:c.234C>A
ENST00000399237.6:c.279C>A
ENST00000399240.5:c.234C>A
ENST00000437180.5:c.315C>A
ENST00000455571.5:c.276C>A
ENST00000482318.5:c.59-6166C>A
NM_001001890.2:c.234C>A
NM_001122607.1:c.234C>A
NM_001001890.3:c.234C>A
NM_001122607.2:c.234C>A
NM_001754.5:c.315C>A

Likely Pathogenic

Met criteria codes 4

PS3 PP3 PM1_Supporting PM2_Supporting

Not Met criteria codes 22

PS1 PS2 PS4 BA1 PP1 PP2 PP4 PM6 PM3 PM5 PM4 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PVS1

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 Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Myeloid Malignancy VCEP

The NM_001754.4:c.315C>A (p.His105Gln) variant affects one of the residues (AA 105-204) within the RHD which is not an established hotspot residue (PM1_Supporting). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). Transactivation assays demonstrating altered transactivation (<20% of wt, and/or reduced to levels similar to well-established pathogenic variants such as R201Q or R166Q) and data from secondary assays demonstrate altered DNA binding and functional consequences in mouse model. (PS3; PMID: 22318203; PMID: 25840971). This missense variant has a REVEL score >0.75 (0.901) (PP3). In summary, this variant meets criteria to be classified as likely pathogenic. ACMG/AMP criteria applied, as specified by the ClinGen Myeloid Malignancy Variant Curation Expert Panel for RUNX1: PS3, PM2_supporting, PP3, PM1_supporting.

Met criteria codes

PS3	✔	Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered DNA binding and functional consequences in mouse model. Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assay demonstrate altered DNA binding. PubMed:25840971 Transactivation assays demonstrate altered transactivation (<20% of WT). Secondary assays demonstrate altered DNA binding and functional consequences in mouse model. H105Q disturbed myeloid differentiation and induced a blast crisis or accelerated phase–like phenotype in mice. PubMed:22318203
PP3	✔	REVEL: 0.901 >0.75
PM1_Supporting	✔	Residue in RUNT domain (105-204aa).
PM2_Supporting	✔	The variant is absent from all population databases.

Not Met criteria codes

PS1	✖	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
PS4	✖	All patients reported in literature with this variant were not confirmed as germline variants (PMID 22318203, PMID 29722345, PMID 25840971, PMID 24030381, PMID 19282830).
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	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
PM6	ℹ	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	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		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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