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Variant: NM_001754.5(RUNX1):c.484_485delinsGC (p.Arg162Ala)

Version: 2.0

CA916084356

3336850 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia and hematologic cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2a550576-958a-4225-ac13-e4f4abd6c845
Approved on: 2026/4/29
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HGVS expressions

NM_001754.5:c.484_485delinsGC
NM_001754.5(RUNX1):c.484_485delinsGC (p.Arg162Ala)
NC_000021.9:g.34880580_34880581delinsGC
CM000683.2:g.34880580_34880581delinsGC
NC_000021.8:g.36252877_36252878delinsGC
CM000683.1:g.36252877_36252878delinsGC
NC_000021.7:g.35174747_35174748delinsGC
NG_011402.2:g.1109131_1109132delinsGC
ENST00000675419.1:c.484_485delinsGC
ENST00000300305.7:c.484_485delinsGC
ENST00000344691.8:c.403_404delinsGC
ENST00000358356.9:c.403_404delinsGC
ENST00000399237.6:c.448_449delinsGC
ENST00000399240.5:c.403_404delinsGC
ENST00000437180.5:c.484_485delinsGC
ENST00000482318.5:c.*74_*75delinsGC
NM_001001890.2:c.403_404delinsGC
NM_001122607.1:c.403_404delinsGC
NM_001754.4:c.484_485delinsGC
NM_001001890.3:c.403_404delinsGC
NM_001122607.2:c.403_404delinsGC

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PP3 PM1_Strong

Not Met criteria codes 23

PVS1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PS1 PS2 PS3 PS4 PM3 PM5 PM4 BA1 PM6 PP1 PP2 PP4

Evidence Links 9

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.484_485delinsGC (p.Arg162Ala) is a missense variant which affects one of the hotspot residues (R162) in the RHD (PM1_strong). A REVEL score is not available for this variant, but multiple in-silico tools (AGVGD, SIFT, and PolyPhen-2) support a deleterious effect (PP3). This variant is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2_supporting). 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: PM1_strong, PP3, PM2_supporting.

Met criteria codes

PM2_Supporting	✔	Absent from gnomAD with a mean coverage of at least 20X (v2 and v3).
PP3	✔	REVEL score is not available, but AGVGD, SIFT, and PolyPhen-2 all agree on a damaging effect. SSF and MES show loss of a putative cryptic donor splice site at c.485.
PM1_Strong	✔	Hotspot variant

“Ten of these amino acids (Arg-80, Lys-83, Arg-135, Arg-139, Arg-142, Lys-167, Thr-169, Asp-171, Arg-174, and Arg-177) were shown in the crystal structures of the RD-CBFβ-DNA ternary complex to make side chain contacts to the DNA bases or the phosphate backbone (45, 47).” **PubMed:12807882**

“In addition, four amino acids located on β9, L9, and β12, including Arg135, Arg139, Gly143, and Lys167 (Arg135 is not shown in Figure 3A for clarity), make direct contacts with the DNA backbone 29, 30… When anchored on the DNA helix, the three “sequence-specific” loops are maintained by “in-line” van der Waals interactions from Pro173 via His78 and Lys167 to the backbone of L9 as well as by a nearly linear array of salt bridge and attractive interactions of the type CH3…O and CH3…NH2 formed by Arg174, Asp171, Val170, and Arg139 (shown in Figure 3A)… Disease-related mutations in amino acids that form nonspecific contacts with the DNA backbone, Arg135Gly [43], Arg139Gln 37, 41, and Arg139Gly [42], should also be attributed to the loss of interactions that support protein loops (L3 by Arg135 and L9 by Arg139) at the protein-DNA interface Figure 3, Figure 4.” **PubMed:12377125**

"The mutations occurring in these residues, such as R80C, R80G, K83Q, K83R, R135K, R135S, R139Q, R139L, D171Y, D171G, and R174Q detected in this study, would result in loss of hydrogen bonding interaction to DNA or disruption of the folding architecture of RUNX1; additional S114P and S114W were supposed to abolish heterodimerization with CBF-β.39" However, the cited article (PMID: 11257229) does not include this variant in its evaluation." **PubMed:19808697**

A computational tool, Hotspot3D, identified a spatial hotspot cluster in RUNX1 that includes Arg162. **PubMed:27294619**

“In Runx1, Arg135 and Arg139 interact with G105–A107 and G4–C6, respectively (green), while Arg80 interacts with A106–T107, and Lys83 interacts with T107, T109, and A7 (yellow).” **PubMed:28231333**

"At the 5′ end of the consensus-binding site, strand βE′ (Arg 135) and loop βA′–B (Lys 83 and Thr 84) contact the phosphate backbone of DNA strand E (T2, T3 and G4) (Fig. 2a)." **PubMed:11276260**

“DNA binding is mediated by 3 loops called loop(βA'-B), loop(βE'-F), and C-terminal tail in the runt domain, and the amino acid residues (Arg80, Lys83, Thr84, Arg135, Arg139, Gly141, Arg142, Gly143, Ile168, Thr169, Val170, Asp171, Arg174, and Arg177) that directly contact the DNA were determined. Half of these residues (Arg80, Lys83, Arg135, Arg139, Asp171, Arg174, and Arg177) were found to be the targets of amino acid replacement by missense mutations in de novo MDS/AML and/or FPD/AML pedigrees in previous reports." **PubMed:12393679**

Arg135 was recurrently mutated in a cohort of 211 AML cases, including p.Arg135Lys, p.Arg135Ser, p.Arg135Gly, and p.Arg135Thr (Fig. 1). **PubMed:23958918**

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	Not applicable
BS1	✖	Absent from gnomAD with a mean coverage of at least 20X (v2 and v3).
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	“The R135 → A change completely abolished DNA binding, even in the presence of CBFβ. The R135 → K mutant retained some activity, but only when CBFβ was added (Figure 3), implying a more significant role for R135 in DNA binding.” PubMed:9533875 □ Yeast one-hybrid assay was for DNA interaction (Fig. 1A), whereas yeast two-hybrid assay was for CBFβ interaction (Fig. 1B); both used lacZ as the reporter gene. R135A severely affected DNA-binding (--) and does not affect binding to CBFβ (++) (Table 1). □ Electrophoretic mobility shift assays (EMSA) were used to measure equilibrium binding constants (biochemical assay) (Fig. 4A). R135A resulted in an 80-fold increase in K2 over wildtype (i.e. impaired DNA binding) (Table IV). R135A also resulted in a 100-fold increase in K4 over wildtype (i.e. reduced affinity between RD-CBFβ and DNA, but not abolished) (Table IV) and the decrease in K2/K4 (9.3 versus 11.8 for WT) indicates that this mutant would make the runt domain slightly less sensitive to allosteric regulation by CBFβ (Table IV) □ Variants that showed comparable CBFβ-binding to WT in the yeast two-hybrid assay (++ in Table I) were subjected to the modified yeast one-hybrid assay. β-galactosidase activity was detectable in the modified yeast one-hybrid assay for R135A with CBFβ (without CBFβ is control) (Fig. 5B) □ R135A seems to perturb the overall structure of the protein by NMR spectroscopy (Table II), so D50 measurements, which represent the concentration of urea at which half of the molecules are unfolded, were performed and showed a lower value compared to WT = “somewhat destabilized” (Table III) PubMed:12807882 R135A demonstrated decreased DNA binding with and without CBFβ (Fig. 4C). PubMed:11276260
BP4	✖	REVEL score is not available (in VCI or Ensembl's VEP), but AGVGD, SIFT, and PolyPhen-2 all agree on a damaging effect.
BP3	✖	Not applicable
BP1	✖	Not applicable
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	Not applicable
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		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	R135A is associated with decreased DNA-binding, but not CBFβ-binding (PMID: 12807882, 11276260, 9533875). "The R135 → A change completely abolished DNA binding, even in the presence of CBFβ. The R135 → K mutant retained some activity, but only when CBFβ was added (Figure 3), implying a more significant role for R135 in DNA binding." PubMed:9533875 Yeast one-hybrid assay was for DNA interaction (Fig. 1A), whereas yeast two-hybrid assay was for CBFβ interaction (Fig. 1B); both used lacZ as the reporter gene. R135A severely affected DNA-binding (--) and does not affect binding to CBFβ (++) (Table 1). Electrophoretic mobility shift assays (EMSA) were used to measure equilibrium binding constants (biochemical assay) (Fig. 4A). R135A resulted in an 80-fold increase in K2 over wildtype (i.e. impaired DNA binding) (Table IV). R135A also resulted in a 100-fold increase in K4 over wildtype (i.e. reduced affinity between RD-CBFβ and DNA, but not abolished) (Table IV) and the decrease in K2/K4 (9.3 versus 11.8 for WT) indicates that this mutant would make the runt domain slightly less sensitive to allosteric regulation by CBFβ (Table IV) Variants that showed comparable CBFβ-binding to WT in the yeast two-hybrid assay (++ in Table I) were subjected to the modified yeast one-hybrid assay. β-galactosidase activity was detectable in the modified yeast one-hybrid assay for R135A with CBFβ (without CBFβ is control) (Fig. 5B) R135A seems to perturb the overall structure of the protein by NMR spectroscopy (Table II), so D50 measurements, which represent the concentration of urea at which half of the molecules are unfolded, were performed and showed a lower value compared to WT = "somewhat destabilized" (Table III) PubMed:12807882 R135A demonstrated decreased DNA binding with and without CBFβ (Fig. 4C). PubMed:11276260
PS4		✖	No case reports of the variant in the literature (ClinVar, HGMD, LOVD, COSMIC).
PM3		✖	Not applicable
PM5		✖	PM1_strong met.
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	Absent from gnomAD with a mean coverage of at least 20X (v2 and v3).
PM6		✖	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		✖	Not applicable
PP4		✖	Not applicable

Curation History

Showing 1 to 2 of 2 rows

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