The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001754.4(RUNX1):c.508+3delA

Version: 1.0

CA248618

14466 (ClinVar)

Gene: RUNX1 (HGNC:861)
Condition: hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome (MONDO:0011071)
Inheritance Mode: Autosomal dominant inheritance
UUID: d7a48ae9-bd50-426d-bb9f-589c53013a9b
Approved on: 2019-08-01
Published on: 2019-08-02

HGVS expressions

NM_001754.4:c.508+3delA
NM_001754.4(RUNX1):c.508+3delA
NC_000021.9:g.34880554del
CM000683.2:g.34880554del
NC_000021.8:g.36252851del
CM000683.1:g.36252851del
NC_000021.7:g.35174721del
NG_011402.2:g.1109158del
ENST00000675419.1:c.508+3del
ENST00000300305.7:c.508+3del
ENST00000344691.8:c.427+3del
ENST00000358356.9:c.427+3del
ENST00000399237.6:c.472+3del
ENST00000399240.5:c.427+3del
ENST00000437180.5:c.508+3del
ENST00000482318.5:c.*98+3del
NM_001001890.2:c.427+3del
NM_001122607.1:c.427+3del
NM_001754.4:c.508+3del
NM_001001890.3:c.427+3del
NM_001122607.2:c.427+3del
NM_001754.5:c.508+3del

Pathogenic

Met criteria codes 5

PS4_Supporting PP1_Strong PP3 PS3 PM2

Not Met criteria codes 21

BA1 PVS1 BP5 BP7 BP4 BP3 BP1 BP2 BS1 BS4 BS3 BS2 PP2 PP4 PM1 PM3 PM5 PM4 PS1 PS2 PM6

Evidence Links 1

Expert Panel

Myeloid Malignancy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Myeloid Malignancy VCEP

There is RT-PCR assay evidence demonstrating that the NM_001754.4:c.508+3delA variant creates a cryptic splice donor site that is used and results in a frameshift and introduction of premature termination codon (PS3; PMID: 11830488). This variant was found to co-segregate with disease in multiple affected family members, with eight meioses observed in one family (PP1_Strong; PMID: 11830488). It is completely absent from all population databases with at least 20x coverage for RUNX1 (PM2). This intronic variant (in intron 5) is located in reference to the exon at positions +3 for donor splice site and have a predicted decrease in the score of the canonical splice site by at least 75% (measured by both MES and SSF). This variant has been reported in one proband meeting at least one of the RUNX1-phenotypic criteria (PS4_Supporting; PMID: 11830488). 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: PS3, PP1_Strong, PM2, PP3, PS4_Supporting.

Met criteria codes

PS4_Supporting	✔	One family with FPD/AML. One family with FPD/AML. PubMed:11830488
PP1_Strong	✔	8 meioses in a family with FPD/AML. 8 meioses in a family with FPD/AML. PubMed:11830488
PP3	✔	Intronic variant (in introns 5) located in reference to exon at positions +3 for donor splice site and have a predicted decrease in the score of the canonical splice site by at least 75% (measured by both MES and SSF)
PS3	✔	RT-PCR assay demonstrates the use of a cryptic splice donor site resulted in frameshift, PMID: 11830488. A 1-bp deletion in the splice donor site of intron 5 of the RUNX1 gene. The novel transcript resulting from use of a cryptic donor site resulted in frameshift after amino acid 135, addition of 41 unrelated residues, and termination at codon 177 (Arg135fsTer177). PubMed:11830488
PM2	✔	The variant is absent from all population databases.

Not Met criteria codes

BA1	✖	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
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	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
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	8 meioses in a family with FPD/AML. PubMed:11830488
BS3	✖	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
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
PM1	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	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
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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