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: NR_003051.3(RMRP):n.-22_-13dup10

Version: 1.1

CA257182

14210 (ClinVar)

Gene: RMRP (HGNC:6023)
Condition: cartilage-hair hypoplasia (MONDO:0009595)
Inheritance Mode: Autosomal recessive inheritance
UUID: 557eeee2-413e-41a4-b13c-f736741c8fa1
Approved on: 2026-02-21
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HGVS expressions

NR_003051.3(RMRP):n.-22_-13dup10
NC_000009.12:g.35658031_35658040dup
CM000671.2:g.35658031_35658040dup
NC_000009.11:g.35658028_35658037dup
CM000671.1:g.35658028_35658037dup
NC_000009.10:g.35648028_35648037dup
NG_017041.1:g.4979_4988dup
NG_033120.1:g.4742_4751dup

Pathogenic

Met criteria codes 5

PM2_Supporting PP4_Moderate PM1_Strong PM4 PM3_Strong

Not Met criteria codes 21

BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2 BA1 PS1 PS2 PS3 PS4 PP1 PP2 PP3 PM6 PVS1 PM5

Evidence Links 0

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RMRP Version 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NC_000009.12:g.35658031_35658040dup variant is a 10-base duplication in the promoter region of RMRP. This variant is also described as NR_003051.3(RMRP):n.-22_-13dup10. No population data was found for this allele in gnomAD v4. (PM2_supporting). The duplication lies within the critical promoter region, between the TATA box (n.-32 to n.-24) and the transcription start site (n.4), consistent with functional importance and the variant also meets PM2 per specification caveat. (PM1_strong). The insertion of 6 or more nucleotides increasing the distance between TATA box (n.-32 to n.-24) and the transcription start site (n.4), which has been shown to disrupt promoter function (PM4_Moderate). Klemetti et al., 2017 (PMID: 28094436) describes 4 patients with CHH that were compound heterozygous for g.70A>G and a 10-nt duplication at position −13 (reported sequence TACTCTGTGA). Patient 1 was the index case and Patients 2–4 were identified from the Finnish Skeletal Dysplasia Register. The g.70A>G (NC_000009.12:g.35657948T>C) variant has been previously classified as pathogenic by the SCID VCEP RMRP group. For Patient 1 "Parents were both heterozygous carriers of one of the mutations" confirming

phase in trans with pathogenic variant (1pt). Phase is not given for patients 2-4 identified in th registry (0.5ptx 3 = 1.5 pts). (PM3_Strong, total 2.5pts) Clinical data shared through internal communication with Dr. Svetlana Vakkilainen describes a patient with CHH from 263G>T /-22_-13dup (patient 21 from PMID: 38187867). In the communication the patient met the following PP4 criteria: diagnostic criteria for SCID (1pt), SCID genetic testing conducted (0.5 pt), metaphyseal dysplasia (1 pt), and T cell lymphopenia (0.5pts). (PP4_Moderate, total 3 points) In summary, this variant is classified as Pathogenic based on the following ACMG/AMP criteria (SCID VCEP RMRP specifications Version 1.1): PM2 Supporting, PM1_strong, PM4_moderate, PM3_Strong, PP4_Moderate).

Met criteria codes

PM2_Supporting	✔	No population data was found for this allele in gnomAD v4. (PM2_supporting).
PP4_Moderate	✔	Clinical data shared through internal communication with Dr. Svetlana Vakkilainen describes a patient with CHH from 263G>T /-22_-13dup (patient 21 from PMID: 38187867). In the communication the patient met the following PP4 criteria: diagnostic criteria for SCID (1pt), SCID genetic testing conducted (0.5 pt), metaphyseal dysplasia (1 pt), and T cell lymphopenia (0.5pts). (PP4_Moderate, total 3 points)
PM1_Strong	✔	The duplication lies within the critical promoter region, between the TATA box (n.-32 to n.-24) and the transcription start site (n.4), consistent with functional importance and the variant also meets PM2 per specification caveat. (PM1_strong).
PM4	✔	The insertion of 6 or more nucleotides increasing the distance between TATA box (n.-32 to n.-24) and the transcription start site (n.4), which has been shown to disrupt promoter function (PM4_Moderate).
PM3_Strong	✔	Klemetti et al., 2017 (PMID: 28094436) describes 4 patients with CHH that were compound heterozygous for g.70A>G and a 10-nt duplication at position −13 (reported sequence TACTCTGTGA). Patient 1 was the index case and Patients 2–4 were identified from the Finnish Skeletal Dysplasia Register. The g.70A>G (NC_000009.12:g.35657948T>C) variant has been previously classified as pathogenic by the SCID VCEP RMRP group. For Patient 1 "Parents were both heterozygous carriers of one of the mutations" confirming phase in trans with pathogenic variant (1pt). Phase is not given for patients 2-4 identified in th registry (0.5ptx 3 = 1.5 pts). (PM3_Strong, total 2.5pts)

Not Met criteria codes

BS2	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	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
BA1	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	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
PP3	ℹ	✖	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

PVS1	✖	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

Curation History

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