Variant: NR_003051.4(RMRP):n.-24_-3dup

Version: 1.0

CA587570196

1454754 (ClinVar)

Gene: N/A
Condition: cartilage-hair hypoplasia (MONDO:0009595)
Inheritance Mode: Autosomal recessive inheritance
UUID: fa606dac-e859-494e-9d3d-afd5d6b163ed
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HGVS expressions

NR_003051.4:n.-24_-3dup
NR_003051.4(RMRP):n.-24_-3dup
NC_000009.12:g.35658023_35658044dup
CM000671.2:g.35658023_35658044dup
NC_000009.11:g.35658020_35658041dup
CM000671.1:g.35658020_35658041dup
NC_000009.10:g.35648020_35648041dup
NG_017041.1:g.4976_4997dup
NG_033120.1:g.4734_4755dup

Pathogenic

Met criteria codes 6

PM2_Supporting | PP4 | PM3_Strong | PM1_Strong | PP1_Moderate | PM4

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 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The NC_000009.12:g.35658023_35658044dup variant is a 22-base duplication upstream of the transcribed region of the RMRP gene. This variant is also known as NR_003051.4(RMRP):n.-24_-3dup or g.–25_–4dup22TACTACTCTGTGAAGCTGAGAA. It locates between the TATA box (spanning n.-32 to n.-24) and the transcription start site (n.4) (PM1_Strong). It inserts 22 nucleotides that increases the distance between the TATA box and the transcription start site (PM4_Moderate). The Grpmax Filtering allele frequency of this variant is 0.000004890 in gnomAD v4.1.0, which is lower than the SCID-VCEP threshold (<0.0000447) for PM2_Supporting (PM2_Supporting). This variant is reported in trans with the variant g.196C>T (previously curated as pathogenic by the SCID VCEP: NC_000009.12:g.35657823G>A) in four Brazilian patients and is reported in trans with the variant g.97_98dup2(TG) (not curated by the SCID VCEP) in one Brazilian patient (+1.0 points each). The total score is 2.0 meeting this criterion PM3_Strong. (PMID: 32021596). Among these cases, two affected siblings have been

described (PP1_Moderate). At least one patient presented with metaphyseal dysplasia (+1.0 points) and hypotrichosis (+0.5 points). PP4 is met. In summary, this variant is classified as pathogenic for Autosomal Recessive Cartilage Hair Hypoplasia based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PM2_Supporting, PM1_Strong, PM4_Moderate, PM3_Strong, PP1_Moderate, PP4 (SCID VCEP specifications version 1).

Met criteria codes

PM2_Supporting ✔	The Grpmax Filtering allele frequency of this variant is 0.000004890 in gnomAD v4.1.0, which is lower than the SCID-VCEP threshold (<0.0000447) for PM2_Supporting. PM2_Supporting is met.
PP4 ✔	At least one patient (patient 2) presented with metaphyseal dysplasia (+1.0 points) and hypotrichosis (+0.5 points). Immunological status for affected patients is not evaluated in this study. Total score is 1.5 points. PP4 is met (PMID: 32021596).
PM3_Strong ✔	This variant is in trans with variant g.196C>T in four Brazilian patients with CHH including two affected siblings (+1.0 points) and in trans with variant g.97_98dup2(TG) in another Brazilian patient with CHH (+1.0 points) (PMID: 32021596), reaching a total of 2.0 points meeting PM3_Strong.
PM1_Strong ✔	This variant locates between the TATA box (spanning n.-32 to n.-24) and the transcription start site (n.4) (PM1_Strong).
PP1_Moderate ✔	This variant has been reported in two affected siblings in trans with the variant g.196C>T.
PM4 ✔	This variant inserts 22 nucleotides that increases the distance between the TATA box (spanning n.-32 to n.-24) and the transcription start site (n.4) (PM4_Moderate).

Curation History

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