Variant: NM_001033855.3(DCLRE1C):c.103C>G (p.His35Asp)

Version: 1.0

CA117007

4674 (ClinVar)

Gene: DCLRE1C (HGNC:64421)
Condition: severe combined immunodeficiency due to DCLRE1C deficiency (MONDO:0011225)
Inheritance Mode: Autosomal recessive inheritance
UUID: 50baf4df-88c8-469b-a6eb-3b8a7fecc340
Approved on: 2024-01-23
Published on: 2024-01-23

HGVS expressions

NM_001033855.3:c.103C>G
NM_001033855.3(DCLRE1C):c.103C>G (p.His35Asp)
NC_000010.11:g.14953908G>C
CM000672.2:g.14953908G>C
NC_000010.10:g.14995907G>C
CM000672.1:g.14995907G>C
NC_000010.9:g.15035913G>C
NG_007276.1:g.5188C>G
ENST00000378241.6:c.103C>G
ENST00000456122.2:c.103C>G
ENST00000489161.2:c.103C>G
ENST00000492201.6:c.103C>G
ENST00000697047.1:c.103C>G
ENST00000697070.1:c.103C>G
ENST00000697071.1:c.103C>G
ENST00000697072.1:c.103C>G
ENST00000697073.1:c.103C>G
ENST00000697074.1:c.103C>G
ENST00000697075.1:c.103C>G
ENST00000697076.1:c.103C>G
ENST00000697077.1:c.103C>G
ENST00000697078.1:c.103C>G
ENST00000697080.1:c.103C>G
ENST00000697081.1:c.103C>G
ENST00000697082.1:c.103C>G
ENST00000697083.1:c.103C>G
ENST00000697084.1:c.103C>G
ENST00000697085.1:c.103C>G
ENST00000697087.1:c.103C>G
ENST00000697088.1:c.103C>G
ENST00000697089.1:c.103C>G
ENST00000697090.1:n.26C>G
ENST00000697091.1:n.164C>G
ENST00000378278.7:c.103C>G
ENST00000357717.6:c.-102C>G

ENST00000378241.5:c.-470C>G
ENST00000378246.6:c.-187C>G
ENST00000378249.5:c.-135C>G
ENST00000378254.5:c.-389C>G
ENST00000378255.5:c.-711C>G
ENST00000378258.5:c.-343C>G
ENST00000378278.6:c.103C>G
ENST00000378289.8:c.103C>G
ENST00000396817.6:c.-665C>G
ENST00000418843.5:c.-426C>G
ENST00000456122.1:c.-594C>G
NM_001033855.2:c.103C>G
NM_001033857.2:c.-343C>G
NM_001033858.2:c.-665C>G
NM_001289076.1:c.-102C>G
NM_001289077.1:c.-389C>G
NM_001289078.1:c.-135C>G
NM_001289079.1:c.-711C>G
NM_022487.3:c.-187C>G
NR_110297.1:n.525C>G
NM_001350965.1:c.103C>G
NM_001350966.1:c.-135C>G
NM_001350967.1:c.-343C>G
NR_146960.1:n.525C>G
NR_146961.1:n.525C>G
NR_146962.1:n.525C>G
NM_001033857.3:c.-343C>G
NM_001033858.3:c.-665C>G
NM_001289076.2:c.-102C>G
NM_001289077.2:c.-389C>G
NM_001289078.2:c.-135C>G
NM_001289079.2:c.-711C>G
NM_001350965.2:c.103C>G
NM_001350966.2:c.-135C>G
NM_001350967.2:c.-343C>G
NM_022487.4:c.-187C>G
NR_110297.2:n.189C>G
NR_146961.2:n.189C>G

Pathogenic

Met criteria codes 5

PP1 **PM2_Supporting** **PS3_Moderate**
PP4_Moderate **PM3_Strong**

Not Met criteria codes 2

PP3 **BS2**

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 DCLRE1C Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

The c.103C>G (NM_001033855.3) variant in DCLRE1C is a missense variant predicted to cause the substitution of Histidine by Aspartic Acid at amino acid 35 (p.His35Asp). The highest population minor allele frequency in gnomAD v4 is 0.000003100 (8/1111884 alleles) in the European (non-Finnish) population, which is lower than the ClinGen SCID VCEP threshold (<0.00003266) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD. Activity levels in % of WT activity = Recombination: Mean (SD): 0 (0.3) and DNA repair (36h after IR): Mean (SD): 27.29 (16.57). PS3 is Met at a moderate level (PMID: 25917813). This variant has been detected in at least 4 individuals with SCID. Of those individuals, 02 were compound heterozygous for the variants: c.2T>C (p.Met1Thr) VUS according to SCID VCEP, 0.25pts AND p.L187*; Pathogenic according to the SCID VCEP specifications, 1 point. 02 individuals were homozygous for the variants (1 point). The total is 2.25 points, PM3_Strong. (PMIDs: 24481607, 15731174, and 32441320). At least one patient with this variant displayed T-B-NK+ (0.5 pts) + Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5 pts) + Family history of SCID (0.5 pts) + SCID gene panel or exome/genome sequencing conducted (0.5 pts), totaling 2 points, which is highly specific for SCID (PP4_Moderate, PMID: 24481607). In summary, this variant is classified as a Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PM3_Strong, PS3_Moderate, PP1_Supporting, PP4_Moderate, and PM2_Supporting.

Met criteria codes

PP1	ℹ	✓	The variant has been reported to segregate with OS in - at least - 02 affected family members (proband + one brother) from one family (PP1_Supporting). The patient also had another affected brother without genomic information; PMID: 15731174.
PM2_Supporting	ℹ	✓	The highest population minor allele frequency in gnomAD v4 is 0.000003100 (8/1111884 alleles) in the European (non-Finnish) population, which is lower than the ClinGen SCID VCEP threshold (<0.00003266) for PM2_Supporting, meeting this criterion (PM2_Supporting). No homozygotes have been observed in gnomAD.
PS3_Moderate	ℹ	✓	Activity levels in % of WT activity = Recombination: Mean (SD): 0 (0.3) and DNA repair (36h after IR): Mean (SD): 27.29 (16.57). PS3 is Met at a moderate level (PMID: 25917813).
PP4_Moderate	ℹ	✓	At least one patient with this variant displayed T-B-NK+ (0.5 pts) + Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met (0.5 pts) + Family history of SCID (0.5 pts) + SCID gene panel or exome/genome sequencing conducted (0.5 pts), totalizing 2 points, which is highly specific for SCID (PP4_Moderate, PMID: 24481607).
PM3_Strong	ℹ	✓	This variant has been detected in at least 4 individuals with SCID. Of those individuals, 02 were compound heterozygous for the variants: c.2T>C (p.Met1Thr) VUS according to SCID VCEP. Phase is confirmed in another paper that describes the same patient: 0.25pts AND p.L187*; Pathogenic according to the SCID VCEP specifications, 1 point. 02 individuals were homozygous for the variants (1 point). The total is 2.25 points, PM3_Strong. (PMIDs: 24481607, 15731174, and 32441320).

Not Met criteria codes

PP3	ℹ	✗	Do not apply to missense variants.
BS2		✗	No homozygotes have been observed in gnomAD.

Curation History

Showing 1 to 1 of 1 rows
