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_001033855.3(DCLRE1C):c.95C>G (p.Ser32Cys)

Version: 1.0

CA376065642

2136852 (ClinVar)

Gene: DCLRE1C (HGNC:64421)
Condition: severe combined immunodeficiency due to DCLRE1C deficiency (MONDO:0011225)
Inheritance Mode: Autosomal recessive inheritance
UUID: 78a7041b-31ae-4b6c-9561-39870c271524
Approved on: 2024/1/23
Published on: 2024/1/23

HGVS expressions

NM_001033855.3:c.95C>G
NM_001033855.3(DCLRE1C):c.95C>G (p.Ser32Cys)
NC_000010.11:g.14953916G>C
CM000672.2:g.14953916G>C
NC_000010.10:g.14995915G>C
CM000672.1:g.14995915G>C
NC_000010.9:g.15035921G>C
NG_007276.1:g.5180C>G
ENST00000378241.6:c.95C>G
ENST00000456122.2:c.95C>G
ENST00000489161.2:c.95C>G
ENST00000492201.6:c.95C>G
ENST00000697047.1:c.95C>G
ENST00000697070.1:c.95C>G
ENST00000697071.1:c.95C>G
ENST00000697072.1:c.95C>G
ENST00000697073.1:c.95C>G
ENST00000697074.1:c.95C>G
ENST00000697075.1:c.95C>G
ENST00000697076.1:c.95C>G
ENST00000697077.1:c.95C>G
ENST00000697078.1:c.95C>G
ENST00000697080.1:c.95C>G
ENST00000697081.1:c.95C>G
ENST00000697082.1:c.95C>G
ENST00000697083.1:c.95C>G
ENST00000697084.1:c.95C>G
ENST00000697085.1:c.95C>G
ENST00000697087.1:c.95C>G
ENST00000697088.1:c.95C>G
ENST00000697089.1:c.95C>G
ENST00000697090.1:n.18C>G
ENST00000697091.1:n.156C>G
ENST00000378278.7:c.95C>G
ENST00000357717.6:c.-110C>G
ENST00000378241.5:c.-478C>G
ENST00000378246.6:c.-195C>G

ENST00000378249.5:c.-143C>G
ENST00000378254.5:c.-397C>G
ENST00000378255.5:c.-719C>G
ENST00000378258.5:c.-351C>G
ENST00000378278.6:c.95C>G
ENST00000378289.8:c.95C>G
ENST00000396817.6:c.-673C>G
ENST00000418843.5:c.-434C>G
ENST00000456122.1:c.-602C>G
NM_001033855.2:c.95C>G
NM_001033857.2:c.-351C>G
NM_001033858.2:c.-673C>G
NM_001289076.1:c.-110C>G
NM_001289077.1:c.-397C>G
NM_001289078.1:c.-143C>G
NM_001289079.1:c.-719C>G
NM_022487.3:c.-195C>G
NR_110297.1:n.517C>G
NM_001350965.1:c.95C>G
NM_001350966.1:c.-143C>G
NM_001350967.1:c.-351C>G
NR_146960.1:n.517C>G
NR_146961.1:n.517C>G
NR_146962.1:n.517C>G
NM_001033857.3:c.-351C>G
NM_001033858.3:c.-673C>G
NM_001289076.2:c.-110C>G
NM_001289077.2:c.-397C>G
NM_001289078.2:c.-143C>G
NM_001289079.2:c.-719C>G
NM_001350965.2:c.95C>G
NM_001350966.2:c.-143C>G
NM_001350967.2:c.-351C>G
NM_022487.4:c.-195C>G
NR_110297.2:n.181C>G
NR_146961.2:n.181C>G

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PP4 PS3_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

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.95C>G (NM_001033855.3) variant in DCLRE1C is a missense variant predicted to cause substitution of Serine by Cysteine at amino acid 32 (p.Ser32Cys). The highest population minor allele frequency in gnomAD v.4 is 0.00002236 (1/44722 alleles) in Latino/Admixed American population, which is lower than the ClinGen SCID VCEP threshold (<0.00003266) for PM2_Supporting, meeting this criterion (PM2_Supporting). Another missense variant, c.95C>T; p.Ser32Phe, ClinVar Variation ID: 1438811, in the same codon, has been classified as likely pathogenic for SCID by the ClinGen SCID VCEP (PM5_Supporting). The variant was identified in two patients in the literature (PubMed IDs 25917813, 15242402, and PMID: 35886058. The patient reported in Rosina E et al. presents: Diagnostic criteria for SCID 0.5 pts + SCID gene panel or exome/genome sequencing conducted 0.5pts + T-B-NK+ lymphocyte subset profile 0.5 pts, total is 1.5 points, PP4_Supporting. This same patient is homozygous for the variant: 0.5 pts, PM3_Supporting (PMID: 35886058). Activity levels in % of WT activity = Recombination: Mean (SD): 0 (0.4) and DNA repair (36h after IR): Mean (SD): 6.56 (8.73). Both values are lower than our established threshold for abnormal results (defined as <25% of wild-type activity). Thus, PS3 is Met at a moderate level (PMID: 25917813). In summary, this variant is classified as Likely Pathogenic for autosomal recessive severe combined immunodeficiency due to DCLRE1C deficiency based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PM2_Supporting, PM5_Supporting, PP4_Supporting, PM3_Supporting, and PS3_Moderate.

Met criteria codes

PM3_Supporting	✔	The patient reported in Rosina E et al. is homozygous for this variants. 0.5 pts, PM3_Supporting (PMID: 35886058).
PP4	✔	The variant was identified in two patients in the literature (PubMed IDs 25917813, 15242402, and PMID: 35886058. The patient reported in Rosina E et al. presents: Diagnostic criteria for SCID 0.5 pts + SCID gene panel or exome/genome sequencing conducted 0.5pts + T-B-NK+ lymphocyte subset profile 0.5 pts, total is 1.5 points, PP4_Supporting. .
PS3_Moderate	✔	Activity levels in % of WT activity = Recombination: Mean (SD): 0 (0.4) and DNA repair (36h after IR): Mean (SD): 6.56 (8.73). Both values are lower than our established threshold for abnormal results (defined as <25% of wild-type activity). Thus, PS3 is Met at a moderate level (PMID: 25917813).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4 is 0.00002236 (1/44722 alleles) in Latino/Admixed American population, which is lower than the ClinGen SCID VCEP threshold (<0.00003266) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM5_Supporting	✔	Another missense variant, c.95C>T; p.Ser32Phe, ClinVar Variation ID: 1438811, in the same codon, has been classified as likely pathogenic for SCID by the ClinGen SCID VCEP (PM5_Supporting).

Not Met criteria codes

BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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