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Variant: NM_001033855.3(DCLRE1C):c.95C>T (p.Ser32Phe)

Version: 1.0

CA203404964

1438811 (ClinVar)

Gene: DCLRE1C (HGNC:64421)
Condition: severe combined immunodeficiency due to DCLRE1C deficiency (MONDO:0011225)
Inheritance Mode: Autosomal recessive inheritance
UUID: ed12e4e0-a9f1-4f0b-858b-8eda63ce5c01
Approved on: 2024/1/23
Published on: 2024/1/23

HGVS expressions

NM_001033855.3:c.95C>T
NM_001033855.3(DCLRE1C):c.95C>T (p.Ser32Phe)
NC_000010.11:g.14953916G>A
CM000672.2:g.14953916G>A
NC_000010.10:g.14995915G>A
CM000672.1:g.14995915G>A
NC_000010.9:g.15035921G>A
NG_007276.1:g.5180C>T
ENST00000378241.6:c.95C>T
ENST00000456122.2:c.95C>T
ENST00000489161.2:c.95C>T
ENST00000492201.6:c.95C>T
ENST00000697047.1:c.95C>T
ENST00000697070.1:c.95C>T
ENST00000697071.1:c.95C>T
ENST00000697072.1:c.95C>T
ENST00000697073.1:c.95C>T
ENST00000697074.1:c.95C>T
ENST00000697075.1:c.95C>T
ENST00000697076.1:c.95C>T
ENST00000697077.1:c.95C>T
ENST00000697078.1:c.95C>T
ENST00000697080.1:c.95C>T
ENST00000697081.1:c.95C>T
ENST00000697082.1:c.95C>T
ENST00000697083.1:c.95C>T
ENST00000697084.1:c.95C>T
ENST00000697085.1:c.95C>T
ENST00000697087.1:c.95C>T
ENST00000697088.1:c.95C>T
ENST00000697089.1:c.95C>T
ENST00000697090.1:n.18C>T
ENST00000697091.1:n.156C>T
ENST00000378278.7:c.95C>T
ENST00000357717.6:c.-110C>T
ENST00000378241.5:c.-478C>T
ENST00000378246.6:c.-195C>T

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

Likely Pathogenic

Met criteria codes 4

PM3 PS3_Moderate PP4 PM2_Supporting

Not Met criteria codes 1

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 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>T (NM_001033855.3) variant in DCLRE1C is a missense variant predicted to cause substitution of Serine by Phenylalanine at amino acid 32 (p.Ser32Phe). The filtering allele frequency (the upper threshold of the 95% CI of 2/1111892 alleles) of the c.95C>T variant in DCLRE1C is 0.0000003 for European (non-Finnish) chromosomes by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.00003266) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). At least one patient in the literature presents: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met 0.5 pts + T-B-NK+ lymphocyte subset profile 0.5 pts, total 1 pt; Which is highly specific for SCID. PP4_Supporting (PMIDs: 18223550 and 25917813 - same patient). The proband is compound heterozygous, in trans, for del Ex1-3 (at least LP according to our SCID VCEP specifications;) 1 point, PM3_Moderate. (PMID: 25917813). Activity levels in % of WT activity = Recombination: Mean (SD): 5.14 (0.34) and DNA repair (36h after IR): Mean (SD): 20.95 (6.17). 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 a Likely Pathogenic for autosomal recessive SCID based on ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP (specification version 1.0): PM2_Supporting, PP4_Supporting, PM3_Moderate, and PS3_Moderate.

Met criteria codes

PM3	✔	Proband is compound heterozygous, in trans, for del Ex1-3 (at least LP according to our SCID VCEP specifications;) 1 point, PM3_Moderate. (PMID: 25917813).
PS3_Moderate	✔	Activity levels in % of WT activity = Recombination: Mean (SD): 5.14 (0.34) and DNA repair (36h after IR): Mean (SD): 20.95 (6.17). 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).
PP4	✔	At least one patient in the literature present: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met 0.5 pts + T-B-NK+ lymphocyte subset profile 0.5 pts, total 1 pt; Which is highly specific for SCID. PP4_Supporting (PMIDs: 18223550 and 25917813 - same patient).
PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 2/1111892 alleles) of the c.95C>T variant in DCLRE1C is 0.0000003 for European (non-Finnish) chromosomes by gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (<0.00003266) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

PM5	✖	NM_001033855.3(DCLRE1C):c.95C>G (p.Ser32Cys) is VUS. Not used here to avoid circularity.

Curation History

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