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Variant: NM_001033855.3(DCLRE1C):c.597C>A (p.Tyr199Ter)

Version: 1.0

CA117004

4673 (ClinVar)

Gene: DCLRE1C (HGNC:64421)
Condition: severe combined immunodeficiency due to DCLRE1C deficiency (MONDO:0011225)
Inheritance Mode: Autosomal recessive inheritance
UUID: c4b37927-7eb1-46bc-bb15-0a307360ce77
Approved on: 2024-03-08
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HGVS expressions

NM_001033855.3:c.597C>A
NM_001033855.3(DCLRE1C):c.597C>A (p.Tyr199Ter)
NC_000010.11:g.14934461G>T
CM000672.2:g.14934461G>T
NC_000010.10:g.14976460G>T
CM000672.1:g.14976460G>T
NC_000010.9:g.15016466G>T
NG_007276.1:g.24635C>A
ENST00000378241.6:c.*644C>A
ENST00000456122.2:c.*783C>A
ENST00000489161.2:c.*375C>A
ENST00000492201.6:c.597C>A
ENST00000697047.1:c.597C>A
ENST00000697070.1:c.597C>A
ENST00000697071.1:c.*517C>A
ENST00000697072.1:c.597C>A
ENST00000697073.1:c.*375C>A
ENST00000697074.1:c.*375C>A
ENST00000697075.1:c.597C>A
ENST00000697076.1:c.597C>A
ENST00000697077.1:c.*308C>A
ENST00000697078.1:c.*304C>A
ENST00000697079.1:n.301C>A
ENST00000697080.1:c.*461C>A
ENST00000697081.1:c.*214C>A
ENST00000697082.1:c.*783C>A
ENST00000697083.1:c.*457C>A
ENST00000697084.1:c.597C>A
ENST00000697085.1:c.*364C>A
ENST00000697086.1:n.3034C>A
ENST00000697087.1:c.*517C>A
ENST00000697088.1:c.*214C>A
ENST00000697089.1:c.*517C>A
ENST00000697090.1:n.605C>A
ENST00000378278.7:c.597C>A

ENST00000357717.6:c.252C>A
ENST00000378241.5:c.237C>A
ENST00000378246.6:c.252C>A
ENST00000378249.5:c.252C>A
ENST00000378254.5:c.237C>A
ENST00000378255.5:c.237C>A
ENST00000378258.5:c.237C>A
ENST00000378278.6:c.597C>A
ENST00000378289.8:c.597C>A
ENST00000396817.6:c.237C>A
ENST00000418843.5:c.159C>A
NM_001033855.2:c.597C>A
NM_001033857.2:c.237C>A
NM_001033858.2:c.237C>A
NM_001289076.1:c.252C>A
NM_001289077.1:c.237C>A
NM_001289078.1:c.252C>A
NM_001289079.1:c.237C>A
NM_022487.3:c.252C>A
NR_110297.1:n.1231C>A
NM_001350965.1:c.597C>A
NM_001350966.1:c.252C>A
NM_001350967.1:c.237C>A
NR_146960.1:n.1019C>A
NR_146961.1:n.1048C>A
NR_146962.1:n.1019C>A
NM_001033857.3:c.237C>A
NM_001033858.3:c.237C>A
NM_001289076.2:c.252C>A
NM_001289077.2:c.237C>A
NM_001289078.2:c.252C>A
NM_001289079.2:c.237C>A
NM_001350965.2:c.597C>A
NM_001350966.2:c.252C>A
NM_001350967.2:c.237C>A
NM_022487.4:c.252C>A
NR_110297.2:n.895C>A
NR_146961.2:n.712C>A

Pathogenic

Met criteria codes 5

PVS1 PM2_Supporting PP4_Moderate PS3_Moderate PM3

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.597C>A (p.Tyr199Ter)(NM_001033855.3) variant in DCLRE1C is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 8/14 leading to nonsense-mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1 is met). The filtering allele frequency (the upper threshold of the 95% CI of 2/350108 alleles) of the c.597C>A variant in DCLRE1C is 0.00000095 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). No homozygotes have been observed in gnomAD. This variant frequently occurs among Athabascan-speaking Native Americans, encompassing the Navajo, Apache, and other indigenous groups in North America. PMID 36546626 shows four occurrences in homozygosity (Patient ART001, Patient ART008, Patient ART009, and Patient ART013), reaching the maximum of 1 point. PM3 is met. Of those, Patient ART001 presents: Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met, 0.5 pt + SCID gene panel or exome/genome sequencing conducted 0.5 pt + Navajo or Apache descent 0.25 pt + SCID phenotype corrected by DCLRE1C gene therapy 1 pt + T-B-NK+ lymphocyte subset 1pt. Total is 3.25 points, PP4_Moderate. Additionally, functional assays show activity levels in % of WT activity = Recombination: Mean (SD): 0.00 (1.21) and DNA repair (36h after IR): Mean (SD): 7.46 (19.56). 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 meets the criteria to be classified as Pathogenic for autosomal recessive severe combined immunodeficiency due to DCLRE1C deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PVS1, PM2_Supporting, PM3, PP4, and PS3_Moderate (VCEP specifications version 1).

Met criteria codes

PVS1	✓	The c.597C>A (p.Tyr199Ter)(NM_001033855.3) variant in DCLRE1C is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 8/14 leading to nonsense-mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1 is met).
PM2_Supporting	✓	The filtering allele frequency (the upper threshold of the 95% CI of 2/350108 alleles) of the c.597C>A variant in DCLRE1C is 0.00000095 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). No homozygotes have been observed in gnomAD.
PP4_Moderate	✓	Diagnostic criteria for SCID/Leaky SCID/Omenn syndrome met, 0.5 pt + SCID gene panel or exome/genome sequencing conducted 0.5 pt + Navajo or Apache descent 0.25 pt + SCID phenotype corrected by DCLRE1C gene therapy 1 pt + T-B-NK+ lymphocyte subset 1pt. Total is 3.25 points, PP4_Moderate.
PS3_Moderate	✓	Activity levels in % of WT activity = Recombination: Mean (SD): 0.00 (1.21) and DNA repair (36h after IR): Mean (SD): 7.46 (19.56). 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).
PM3	✓	This pathogenic variant frequently occurs among Athabascan-speaking Native Americans, encompassing the Navajo, Apache, and other indigenous groups in North America. PMID 36546626 shows four occurrences in homozygosity (Patient ART001, Patient ART008, Patient ART009, and Patient ART013), reaching the maximum of 1 point. PM3 is met.

Curation History

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