

Variant: NM_001033855.3(DCLRE1C):c.406G>A
(p.Asp136Asn)

Version: 1.0

CA376060149 [↗](#)

986350 (ClinVar) [↗](#)

Gene: DCLRE1C ([HGNC:64421](#))

Condition: severe combined immunodeficiency due to DCLRE1C deficiency
([MONDO:0011225](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: aed80e86-ea3c-4172-b541-c4485bd82b0f

Approved on: 2024/1/17

Published on: 2024/1/17

HGVS expressions

NM_001033855.3(DCLRE1C):c.406G>A (p.Asp136Asn)

NM_001033855.3:c.406G>A

NC_000010.11:g.14935521C>T

CM000672.2:g.14935521C>T

NC_000010.10:g.14977520C>T

CM000672.1:g.14977520C>T

NC_000010.9:g.15017526C>T

NG_007276.1:g.23575G>A

ENST00000378241.6:c.*453G>A

ENST00000456122.2:c.*592G>A

ENST00000489161.2:c.*184G>A

ENST00000492201.6:c.406G>A

ENST00000697047.1:c.406G>A

ENST00000697070.1:c.406G>A

ENST00000697071.1:c.*326G>A

ENST00000697072.1:c.406G>A

ENST00000697073.1:c.*184G>A

ENST00000697074.1:c.*184G>A

ENST00000697075.1:c.406G>A

ENST00000697076.1:c.406G>A

ENST00000697077.1:c.*117G>A

ENST00000697078.1:c.*113G>A

ENST00000697079.1:n.110G>A

ENST00000697080.1:c.*270G>A

ENST00000697081.1:c.*23G>A

ENST00000697082.1:c.*592G>A

ENST00000697083.1:c.*266G>A

ENST00000697084.1:c.406G>A

ENST00000697085.1:c.*173G>A

ENST00000697086.1:n.2843G>A

ENST00000697087.1:c.*326G>A

ENST00000697088.1:c.*23G>A

ENST00000697089.1:c.*326G>A

ENST00000697090.1:n.414G>A

ENST00000378278.7:c.406G>A

ENST00000357717.6:c.61G>A
ENST00000378241.5:c.46G>A
ENST00000378246.6:c.61G>A
ENST00000378249.5:c.61G>A
ENST00000378254.5:c.46G>A
ENST00000378255.5:c.46G>A
ENST00000378258.5:c.46G>A
ENST00000378278.6:c.406G>A
ENST00000378289.8:c.406G>A
ENST00000396817.6:c.46G>A
ENST00000418843.5:c.-33G>A
ENST00000456122.1:c.61G>A
NM_001033855.2:c.406G>A
NM_001033857.2:c.46G>A
NM_001033858.2:c.46G>A
NM_001289076.1:c.61G>A
NM_001289077.1:c.46G>A
NM_001289078.1:c.61G>A
NM_001289079.1:c.46G>A
NM_022487.3:c.61G>A
NR_110297.1:n.1040G>A
NM_001350965.1:c.406G>A
NM_001350966.1:c.61G>A
NM_001350967.1:c.46G>A
NR_146960.1:n.828G>A
NR_146961.1:n.857G>A
NR_146962.1:n.828G>A
NM_001033857.3:c.46G>A
NM_001033858.3:c.46G>A
NM_001289076.2:c.61G>A
NM_001289077.2:c.46G>A
NM_001289078.2:c.61G>A
NM_001289079.2:c.46G>A
NM_001350965.2:c.406G>A
NM_001350966.2:c.61G>A
NM_001350967.2:c.46G>A
NM_022487.4:c.61G>A
NR_110297.2:n.704G>A
NR_146961.2:n.521G>A

Likely Pathogenic

Met criteria codes 4

- PM3_Strong
- PS3_Moderate
- PP4
- PM2_Supporting

Not Met criteria codes 4

- BP4
- BP1
- PP2
- PP3

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 NM_001033855.3:c.406G>A variant in DCLRE1C is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 136 (p.Asp136Asn). This variant is absent from population databases (gnomAD v2.2.1) (PM2_Supporting) and has been observed in two probands with SCID that carried a co-occurring variant in trans. The first proband has a clinical diagnosis of severe combined immunodeficiency (SCID) (0.5p) with a T-B-NK+ immunophenotype (0.5p) who was tested using a large 407 gene immunodeficiency panel (0.5p) and carried a co-occurring variant (c.629del p.Tyr210Leufs*14) in trans (Invitae, PP4 1.5p). The second proband is patient ART007 reported in PMID: 36566626, who has a clinical diagnosis of Artemis-related SCID (0.5p) that was corrected by DLCRE1C lentiviral gene therapy (1p) and carried a co-occurring variant (Deletion of exons 1-5) in trans (PP4 1.5p). For both patients, the co-occurring variant was confirmed in trans and would be classified as Likely Pathogenic or Pathogenic (PM3_Strong, 2p (1p per proband)). An in vitro study reported that this variant exhibited < 25% of wildtype V(D)J recombinase activity as well as undetectable endonucleolytic cleavage activity in an in vitro cleavage assay (PMID: 15071507, PS3_Moderate). In summary, this variant is classified as Likely Pathogenic for autosomal recessive SCID based on the ACMG criteria applied, PP4, PM3_Strong, PS3_Moderate, PM2_Supporting, as specified by the ClinGen SCID VCEP (VCEP specifications version 1).

Met criteria codes

PM3_Strong			2 patients reported. 1) This variant identified in 1 white/Causasian patient at Invitae with clinical diagnosis of SCID meeting PP4 criteria. Variant heterozygous, co-occurs in trans with c.629del (p.Tyr210Leufs*14). Variants confirmed in trans via parental testing. No alternate cause for disease identified, 407 gene immunodeficiency panel ordered which included all known SCID genes. The co-occurring variant c.629del (p.Tyr210Leufs*14) is absent from gnomAD (PM2) and is a frameshift variant occurring in exon 8 out of 14 (PVS1 - frameshift variant predicted to undergo NMD in a LOF gene). PM2 + PVS1 alone is enough to classify c.629del (p.Tyr210Leufs*14) as LP, but we also additionally can apply PP4 to the variant as well. Therefore, the co-occurring variant is at least LP and is confirmed in trans with our variant in this patient. This is worth 1 point under SVI recommendation for PM3. 2) This variant identified in 1 while/Caucasian patient in PMID: 36546626 (ART007) meeting PP4 criteria. Variant co-occurs with Deletion (Exons 1-5). Inclusion criteria for cohort reported in this paper included that patient must have mutation of both alleles, therefore the variants are in trans. Deletion (Exons 1-5) has not yet been interpreted by the SCID VCEP, but this variant would be at least LP since it is a CNV that deletes the first 5 exons of the gene, which would include the initiator codon and several missense variants located in this region have been classified as LP or P by the SCID VCEP (p.Ile16Thr and p.Thr65Ile for example). Adding 1 point for in trans with LP/P for patient ART007. Therefore between these 2 patients we have 2 points total and PM3_Strong can be applied to our variant.
PS3_Moderate			PMID: 15071507 demonstrates that this variant has < 25% activity in an in vitro V(D)J recombination assay. This variant also showed undetectable endonucleolytic cleavage activity in an in vitro cleavage assay. This variant therefore qualifies for PS3 at the moderate level (PM3_Moderate criteria: Abnormal result in both an in vitro DNA repair activity assay AND an in vitro V(D)J recombination assay (defined as <25% of wild type activity))
PP4			2 patients identified: 1) This variant identified in 1 white/Causasian patient at Invitae with clinical diagnosis of SCID (diagnostic criteria for SCID met 0.5 points), large 407 gene immunodeficiency panel ordered which included all known SCID genes (0.5 points). Reported lymphocyte profile was T-B-NK+ (0.5p). Variant heterozygous, co-occurs in trans with c.629del (p.Tyr210Leufs*14). No alternate cause for disease identified. Total points for PP4 for patient 1 = 1.5 points. . 2) Patient ART007 in PMID: 36546626 - white/Caucasian patient with ART-SCID that was corrected by lentiviral gene therapy (1p). Supplemental file lists inclusion criteria for cohort reported in this paper and all patients met diagnostic criteria for SCID (0.5p). Total points for patient 2 for PP4 = 1.5 points. So using either patient, PP4 is met at regular strength (no modification)
PM2_Supporting			Variant is absent in gnomAD. ClinGen SCID VCEP uses PM2 at supporting level only.

Not Met criteria codes

BP4		ClinGen SCID VCEP does not apply this code for this gene
BP1		ClinGen SCID VCEP does not apply this code for this gene
PP2		ClinGen SCID VCEP does not apply this code for this gene
PP3	 	ClinGen SCID VCEP does not apply this code for missense variants in this gene

Curation History

	▼	▼
--	---	---

Showing 1 to 1 of 1 rows



The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.