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Variant: NM_002185.5(IL7R):c.379G>A (p.Val127Ile)

Version: 1.0

CA359428682

1339483 (ClinVar)

Gene: IL7R (HGNC:3575)
Condition: severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-positive (MONDO:0012163)
Inheritance Mode: Autosomal recessive inheritance
UUID: 577ca02a-d27e-42e8-86e0-4f997bb220da
Approved on: 2024/2/1
Published on: 2024/2/1

HGVS expressions

NM_002185.5:c.379G>A
NM_002185.5(IL7R):c.379G>A (p.Val127Ile)
NC_000005.10:g.35867463G>A
CM000667.2:g.35867463G>A
NC_000005.9:g.35867565G>A
CM000667.1:g.35867565G>A
NC_000005.8:g.35903322G>A
NG_009567.1:g.15575G>A
ENST00000303115.8:c.379G>A
ENST00000303115.7:c.379G>A
ENST00000506850.5:c.379G>A
ENST00000511031.1:n.513G>A
ENST00000511982.1:c.379G>A
ENST00000514217.5:c.379G>A
NM_002185.3:c.379G>A
NR_120485.1:n.482G>A
NM_002185.4:c.379G>A
NR_120485.2:n.508G>A
NR_120485.3:n.466G>A

Pathogenic

Met criteria codes 4

PM3_Supporting PP4 PVS1 PM2_Supporting

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 IL7R Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

NM_002185.5(IL7R):c.379G>A is a missense variant predicted to cause substitution of Valine by Isoleucine at amino acid 127 (p.Val127Ile). The highest population minor allele frequency in gnomAD v4 is 0.00002991 (1/33436) in African/African American population which is lower than the ClinGen SCID VCEP threshold (<0.00004129) for PM2_Supporting, meeting this criterion (PM2_Supporting). c.379G>A mutation in IL7R abolishes splicing of exons 3-4 and replaces it with splicing of exons 2-4, which introduces a STOP site resulting in premature termination of IL-7Ra translation (Nonsense mediated decay) (PVS1) PMID: 35418989. Female patient with SCID (0.5 pt.), reduced CD127 expression demonstrated by flow cytometry (1 pt.),T-B+NK+ lymphocyte subset profile (0.25 pt.) Total :1.75 pts. (PP4_met ; PMID: 35418989).The patient (PMID: 35418989) was found homozygous for the mutation (0.5 pt.) (PM3_supporting). In summary, this variant meets the criteria to be classified as a Pathogenic variant for autosomal recessive severe combined immunodeficiency due to IL7R deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PM2_supporting,PVS1, PP4_met,PM3_supporting (VCEP specifications version 1).

Met criteria codes

PM3_Supporting	✔	The patient (PMID: 35418989) was found homozygous for the mutation (0.5 pt) (PM3_supporting)
PP4	✔	Female patient with SCID (0.5 pt.), reduced CD127 expression demonstrated by flow cytometry (1 pt.),T-B+NK+ lymphocyte subset profile (0.25 pt.) Total :1.75 pts. (PP4_met ; PMID: 35418989)
PVS1	✔	c.379G>A mutation in IL7R abolishes splicing of exons 3-4 and replaces it with splicing of exons 2-4, which introduces a STOP site resulting in premature termination of IL-7Ra translation (Non sense mediated decay) (PVS1). PMID: 35418989
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4 is 0.00002991 (1/33436) in African/African American population which is lower than the ClinGen SCID VCEP threshold (<0.00004129) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

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