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Variant: NM_002185.5(IL7R):c.353G>A (p.Cys118Tyr)

Version: 1.0

CA214043

36392 (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: 27622bc8-a3f6-4be1-8586-efaffc7e60b2
Approved on: 2024/1/17
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HGVS expressions

NM_002185.5:c.353G>A
NM_002185.5(IL7R):c.353G>A (p.Cys118Tyr)
NC_000005.10:g.35867437G>A
CM000667.2:g.35867437G>A
NC_000005.9:g.35867539G>A
CM000667.1:g.35867539G>A
NC_000005.8:g.35903296G>A
NG_009567.1:g.15549G>A
ENST00000303115.8:c.353G>A
ENST00000303115.7:c.353G>A
ENST00000506850.5:c.353G>A
ENST00000511031.1:n.487G>A
ENST00000511982.1:c.353G>A
ENST00000514217.5:c.353G>A
NM_002185.3:c.353G>A
NR_120485.1:n.456G>A
NM_002185.4:c.353G>A
NR_120485.2:n.482G>A
NR_120485.3:n.440G>A

Pathogenic

Met criteria codes 4

PM2_Supporting | PP1 | PP4_Moderate | PM3_Very Strong

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

The missense variant NM_002185.5(IL7R):c.353G>A (p.Cys118Tyr) occurs at a low filtering allele frequency of 0.000009610 in gnomAD v2.1.1 (<0.00004129; PM2_Supporting). At least 14 SCID or Omenn syndrome patients have been reported with this variant in 10 publications (PMIDs: 35503492, 34573280, 27593400, 24759676, 16492442,15661025, 34153518, 17827065, 24578017, 27833609). Several have highly specific phenotypes which meet criteria for PP4 (PMIDs: 35503492, 24759676) and one patient (PMID: 27833609) had sufficient information to meet PP4_moderate; this patient fulfilled clinical and immunological parameters for severe combined immunodeficiency (SCID), with at T-B+NK+ subtype, absence of CD127 expression, and reduced f IL-7 induced pSTAT5 (Y694) in T-cells, which together are highly specific for IL7R-related SCID (PP4_moderate). Additionally, the variant has been reported to segregate with SCID in 2 affected family members from family 2 in PMID: 15661025 (PP1). Of the 14 patients, eight patients have been reported homozygous for this variant (PMIDs: 35503492, 34573280, 27593400, 24759676, 16492442,15661025; PM3) and six compound heterozygous; second variants were reported in P19 (PMID: 35503492) and the SCID patient reported in Zago CA et al. (PMID: 24759676) both harboring c.361dup without confirmation of trans phase (classified Pathogenic by the SCID VCEP; 0.5+0.5pt), the patients reported by Tsilifis C et al. (PMID: 34153518) and Butte MJ et al. (PMID: 17827065) both harbor c.379+288G>A confirmed in trans (provisionally classified by the SCID VCEP as VUS; 0.25+0.25pt), Case 1 (PMID: 24578017) has c.83-2A>T without confirmation of trans phase (provisionally classified as Pathogenic by the SCID VCEP; 0.5pt), and the patient reported by Gallego-Bustos F et al. (PMID: 27833609) has c.333T>A confirmed in trans (provisionally classified Likely Pathogenic by the SCID VCEP; 1pt), Total=4pts (PM3_VeryStrong). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive SCID based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PM2_supporting, PM3_VeryStrong, PP1, PP4_moderate. (SCID VCEP specifications version 1.0).

Met criteria codes

PM2_Supporting	✔	The filtering allele frequency based on the Latino/Admixed American population (upper bound of 95% CI of 2/34488 observed alleles) is 0.000009610 in gnomAD v2.1.1 which is below the SCID-VCEP threshold (<0.00004129) and therefore meets this criterion (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with SCID in 2 affected family members from family 2 in PMID: 15661025 (estimated LOD 0.6; PP1).
PP4_Moderate	✔	At least 14 SCID or Omenn syndrome patients have been reported with this variant in 10 publications (PMIDs: 35503492, 34573280, 27593400, 24759676, 16492442,15661025, 34153518, 17827065, 24578017, 27833609). Several have highly specific phenotypes which meet criteria for PP4 (PMIDs: 35503492, 24759676) and one patient (PMID: 27833609) had sufficient information to meet PP4_moderate, this patient fulfilled clinical and immunological parameters for severe combined immunodeficiency (SCID), with at T-B+NK+ subtype, absence of CD127 expression, and reduced IL-7 induced pSTAT5 (Y694) in T-cells, which together are highly specific for IL7R-related SCID.
PM3_Very Strong	✔	At least eight patients have been reported homozygous for this variant (PMIDs: 35503492, 34573280, 27593400, 24759676, 16492442,15661025; maximum homozygous contribution to score of 1pt). Additionally, at least six compound heterozygotes have also been reported; second variants were reported in P19 (PMID: 35503492) and the SCID patient reported in Zago CA et al. (PMID: 24759676) both harboring c.361dup without confirmation of trans phase (classified Pathogenic by the SCID VCEP; 0.5+0.5pt), the patients reported by Tsilifis C et al. (PMID: 34153518) and Butte MJ et al. (PMID: 17827065) both harbor c.379+288G>A confirmed in trans (provisionally classified by the SCID VCEP as VUS; 0.25+0.25pt), Case 1 (PMID: 24578017) has c.83-2A>T without confirmation of trans phase (provisionally classified as Pathogenic by the SCID VCEP; 0.5pt), and the patient reported by Gallego-Bustos F et al. (PMID: 27833609) has c.333T>A confirmed in trans (provisionally classified Likely Pathogenic by the SCID VCEP; 1pt), Total=4pts; PM3_VeryStrong

Curation History

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