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Variant: NM_002185.5(IL7R):c.662G>T (p.Ser221Ile)

Version: 1.0

CA160099

134528 (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: 8807c445-1d4b-43e2-b30c-b35866cedc32
Approved on: 2024/1/23
Published on: 2024/11/18

HGVS expressions

NM_002185.5(IL7R):c.662G>T (p.Ser221Ile)
NM_002185.5:c.662G>T
NC_000005.10:g.35873604G>T
CM000667.2:g.35873604G>T
NC_000005.9:g.35873706G>T
CM000667.1:g.35873706G>T
NC_000005.8:g.35909463G>T
NG_009567.1:g.21716G>T
ENST00000303115.8:c.662G>T
ENST00000303115.7:c.662G>T
ENST00000505093.1:c.71G>T
ENST00000506850.5:c.662G>T
ENST00000509668.1:n.404G>T
ENST00000514217.5:c.538-1908G>T
NM_002185.3:c.662G>T
NR_120485.1:n.641-1908G>T
NM_002185.4:c.662G>T
NR_120485.2:n.667-1908G>T
NR_120485.3:n.625-1908G>T

Pathogenic

Met criteria codes 3

PP4 PM3_Very Strong PM2_Supporting

Not Met criteria codes 7

PS1 PS2 PS3 PP1 PM6 PM5 BS3

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 c.662G>T (NM_002185.5) variant in IL7R is a missense variant predicted to cause substitution of Serine by Isoleucine at amino acid 221 (p.Ser221Ile). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). PMID 17201233: Twin B was diagnosed with SCID and was homozygous for this variant. A fraternal twin A with SCID was also reported, but the genotype of this twin was not reported. PMID 18641513: Three individuals were diagnosed with SCID and were homozygous for this variant. This variant has been detected in 7 individuals with SCID. Four individuals were homozygous for the variant (1pt maximum, PMIDs 17201233, 18641513). Two individuals recorded in the Invitae internal database were heterozygous for this variant and a c.83-2A>T variant. The c.83-2A>T variant is classified as pathogenic following the SCID-VCEP specification. The trans phase was confirmed in one patient but not the other (1.5pt in total). One individual, also from Invitae internal database, was heterozygous for this variant and a c.707-2A>G variant. The c.707-2A>G variant is classified as a pathogenic variant following the SCID-VCEP specification. The trans phase was not confirmed in this patient (0.5pt). 4pt in total, PM3_very strong is met. The individual with this variant and c.707-2A>G variant showed a T-B+NK+ lymphocyte profile, and abnormal newborn TREC result, and a diagnosis of SCID. A comprehensive SCID and CID panel did not identify an alternative cause of the disease. 1.25pt for PP4 and PP4 is met (PP4). In summary, this variant meets the criteria to be classified as pathogenic for SCID. ACMG/AMP criteria applied, as specified by the ClinGen SCID-VCEP: PM2_Supporting, PM3_Very strong, PP4. (VCEP specifications version 1).

Met criteria codes

PP4	✔	One individual recorded in the Invitae internal database was diagnosed with SCID. The individual was heterozygous for this variant and a c.707-2A>G variant. The patient showed a T-B+NK+ lymphocyte profile (0.25pt) with an abnormal newborn TREC result and diagnosis of SCID (0.5pt). A comprehensive SCID and CID panel with 130 genes were tested, and no alternative cause of the disease was identified (0.5pt). 1.25pt in total and PP4 is met.
PM3_Very Strong	✔	PMID 17201233: Twin B was diagnosed with SCID and was homozygous for this variant. A fraternal twin A with SCID was also reported, but the genotype of this twin was not reported. PMID 18641513: Three individuals were diagnosed with SCID and were homozygous for this variant. This variant has been detected in 7 individuals with SCID. Four individuals were homozygous for the variant (1pt maximum, PMIDs 17201233, 18641513). Two individuals recorded in the Invitae internal database were heterozygous for this variant and a c.83-2A>T variant. The c.83-2A>T variant is classified as pathogenic following the SCID-VCEP specification. The trans phase was confirmed in one patient but not the other (1.5pt in total). One individual, also from Invitae internal database, was heterozygous for this variant and a c.707-2A>G variant. The c.707-2A>G variant is classified as a pathogenic variant following the SCID-VCEP specification. The trans phase was not confirmed in this patient (0.5pt). 4pt in total, PM3_very strong is met.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP1		✖	In one report, two fraternal twins were diagnosed with SCID. Only one twin was confirmed homozygous for this variant, while the genetic information of the other twin is not reported. PP1 is not met (PMID 17201233).
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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