Variant: NM_000206.3(IL2RG):c.670C>T (p.Arg224Trp)

CA358778

225194 (ClinVar)

Gene: IL2RG (HGNC:3561)
Condition: T-B+ severe combined immunodeficiency due to gamma chain deficiency (MONDO:0010315)
Inheritance Mode: X-linked inheritance
UUID: 20eae169-0d74-4c7c-ab5c-ece464898a11
Approved on: 2024-03-08
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HGVS expressions

NM_000206.3:c.670C>T
NM_000206.3(IL2RG):c.670C>T (p.Arg224Trp)
NC_000023.11:g.71109315G>A
CM000685.2:g.71109315G>A
NC_000023.10:g.70329165G>A
CM000685.1:g.70329165G>A
NC_000023.9:g.70245890G>A
NG_009088.1:g.7239C>T
NG_021141.1:g.2474C>T
ENST00000482750.6:c.670C>T
ENST00000696903.1:n.721C>T
ENST00000374202.7:c.670C>T
ENST00000642473.1:n.1034C>T
ENST00000644022.1:n.936C>T
ENST00000644708.1:n.1076C>T
ENST00000644911.1:n.1076C>T
ENST00000645266.1:c.670C>T
ENST00000645518.1:c.670C>T
ENST00000646106.1:c.670C>T
ENST00000646505.1:c.670C>T
ENST00000647492.1:c.670C>T
ENST00000276110.6:n.1263C>T
ENST00000374188.7:c.-47C>T
ENST00000374202.6:c.670C>T
ENST00000456850.6:c.100C>T
ENST00000464642.5:c.538C>T
ENST00000482750.5:c.83C>T
ENST00000512747.3:n.597C>T
NM_000206.2:c.670C>T

Pathogenic

Met criteria codes 5

PS4 **PP4** **PS3_Supporting**
PM1_Strong **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 IL2RG 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_000206.3:c.670C>T variant in IL2RG is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 224 (p.Arg226Trp). The variant has been observed in at least 10 male probands with SCID (PMIDs 28747913, 21184155, 10792291, 9633906, 9058718, 9049783) (PS4). Among these probands, one proband hemizygous for this variant was diagnosed with SCID and presented a T-B+NK- lymphocyte profile (PMID 9049783) (PP4). The variant is absent from gnomAD v4.0 (PM2_Supporting). The variant affects CpG dinucleotides at c.670C, which is defined as a mutational hotspot by the ClinGen SCID VCEP (PMID 7668284) (PM1_Strong). Surface expression of the IL-2 receptor gamma chain in patient B cells showed that the variant causes decreased surface localization of the protein, indicating that this variant impacts protein function (PMID 9058718)(PS3_Supporting). 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: PM1_Strong, PS4, PP4_Supporting, PM2_Supporting, PS3_Supporting. (VCEP specifications version 1.0)

Met criteria codes

PS4	✓	This variant has been reported in 9 probands meeting the PP4 criteria for SCID. 10pts for PP4 in total, PS4 default strength is met.
PP4	✓	Two male siblings (0.5pt) from one family were hemizygous for this variant and were diagnosed with SCID (0.5pt). Both probands presented a T-B+NK- lymphocyte profile. 1.5pt for PP4, PP4 is met.
PS3_Supporting	✓	Surface expression of the IL-2 receptor gamma chain in patient B cells showed that the variant causes compromised surface localization of the protein, indicating that this variant impacts protein function (PMID 9058718) (PS3_Supporting).
PM1_Strong	✓	This variant affects CpG dinucleotides at c.670C, which is defined as a mutational hotspot by the ClinGen SCID VCEP. (PM1_Strong)
PM2_Supporting	✓	This variant is absent from gnomAD v4.0. (PM2_Supporting)

Curation History

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene

No matching records found
