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Variant: NM_000206.3(IL2RG):c.676C>T (p.Arg226Cys)

Version: 1.0

CA358784

225195 (ClinVar)

Gene: IL2RG (HGNC:3561)
Condition: T-B+ severe combined immunodeficiency due to gamma chain deficiency (MONDO:0010315)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 23b8665a-973b-4fee-9486-bd8769d320c9
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HGVS expressions

NM_000206.3(IL2RG):c.676C>T (p.Arg226Cys)
NM_000206.3:c.676C>T
NC_000023.11:g.71109309G>A
CM000685.2:g.71109309G>A
NC_000023.10:g.70329159G>A
CM000685.1:g.70329159G>A
NC_000023.9:g.70245884G>A
NG_009088.1:g.7245C>T
NG_021141.1:g.2480C>T
ENST00000482750.6:c.676C>T
ENST00000696903.1:n.727C>T
ENST00000374202.7:c.676C>T
ENST00000642473.1:n.1040C>T
ENST00000644022.1:n.942C>T
ENST00000644708.1:n.1082C>T
ENST00000644911.1:n.1082C>T
ENST00000645266.1:c.676C>T
ENST00000645518.1:c.676C>T
ENST00000646106.1:c.676C>T
ENST00000646505.1:c.676C>T
ENST00000647492.1:c.676C>T
ENST00000276110.6:n.1269C>T
ENST00000374188.7:c.-41C>T
ENST00000374202.6:c.676C>T
ENST00000456850.6:c.106C>T
ENST00000464642.5:c.544C>T
ENST00000482750.5:c.89C>T
ENST00000512747.3:n.603C>T
NM_000206.2:c.676C>T

Pathogenic

Met criteria codes 6

PM6 PM1_Strong PS3_Supporting PS4 PM2_Supporting PP4

Not Met criteria codes 2

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

PM5 PP3

Evidence Links 1

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(IL2RG):c.676C>T (p.Arg226Cys) missense variant resides within a CpG dinucleotide region, cDNA 676-677 encoding amino acid R226, of IL2RG that is defined as a mutational hotspot (PMID: 7668284; PM1_Strong). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The male (0.5pt) patient of PMID: 14966353 has a T-B+NK- lymphocyte subset profile (0.5pt) [CD3: 2.5%; CD19: 95.4%; CD16/CD56: 0.5%] which is specific for SCID due to gamma chain deficiency (1pt; PP4). In a second case, the R226C variant arose de novo as a somatic mutation early in embryogenesis in the mother of the patient, 1 pt, PM6_Moderate (PMID: 23683512). At least eight additional male X-SCID patients have been reported (PMIDs: 9058718, 11129345, 22936741, 7668284) with this hemizygous variant (total 4.5pt; PS4). PMID: 7632950 Examined the mutant 7 chain distribution by confocal microscopy in transiently transfected COS-7 cells, comparing it with the wild-type 7 chain distribution. The mutant 7 chain could not be detected by an antihuman IL-2 receptor 7 chain monoclonal antibody, TUGh4, on the cell surface of the transfected COS-7 cells. This result was in sharp contrast to that obtained with the wild-type γ chain, which was clearly stained by TUGh4 on the transfected cells. PS3_Supporting is met. In summary, this variant meets the criteria to be classified as Pathogenic for X-linked T-B+ severe combined immunodeficiency due to gamma chain deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP. Criteria applied: PS4, PM1_Strong, PM6_Moderate, PM2_Supporting, PS3_Supporting, and PP4. (VCEP specifications version 1).

Met criteria codes

PM6 ✔

The R226C variant arose de novo as a somatic mutation early in embryogenesis in the mother of the patient. The IL2RG variant was not detected in the patient's maternal grandparents, supporting the de novo nature of the mother's somatic mosaicism. As somatic mosaicism is observed, maternity/paternity testing is unnecessary to confirm de novo occurrence given the de novo process is observed in the individual directly. So the full points can be awarded in this case. PMID: 23683512; 1 pt PM6_Moderate.

PM1_Strong ✔

This variant resides within a CpG dinucleotide region, cDNA 676-677 encoding amino acid R226, of IL2RG that is defined as a mutational hotspot (PMID: 7668284) critical functional domain by the ClinGen SCID VCEP (PM1_Strong).

PS3_Supporting ✔

PMID: 7632950 Examined the mutant 7 chain distribution by confocal microscopy in transiently transfected COS-7 cells, comparing it with the wild-type 7 chain distribution. The mutant 7 chain could not be detected by an antihuman IL-2 receptor 7 chain monoclonal antibody, TUGh4, on the cell surface of the transfected COS-7 cells. This result was in sharp contrast to that obtained with the wild-type γ chain, which was clearly stained by TUGh4 on the transfected cells. PS3_Supporting is met.

Examined the mutant 7 chain distribution by confocal microscopy in transiently transfected COS-7 cells, comparing it with the wild-type 7 chain distribution. The mutant 7 chain could not be detected by an antihuman IL-2 receptor 7 chain monoclonal antibody, TUGh4, on the cell surface of the transfected COS-7 cells. This result was in sharp contrast to that obtained with the wild-type γ chain, which was clearly stained by TUGh4 on the transfected cells.

PubMed:7632950

PS4		✔	At least eight additional male X-SCID patients have been reported (PMIDs: 9058718, 11129345, 22936741, 7668284) with this hemizygous variant (total 4.5pt; PS4).
PM2_Supporting		✔	This variant is absent from gnomADv2.1.1 (PM2_Supporting).
PP4		✔	The male (0.5pt) patient of PMID: 14966353 has a T-B+NK- lymphocyte subset profile 0.5pt [CD3: 2.5%; CD19: 95.4%; CD16/CD56: 0.5%]. This is specific for SCID due to gamma chain deficiency (1pt; PP4).

Not Met criteria codes

PM5		✖	The additional variant Arg226His has been identified at this amino acid residue but has not yet been evaluated by the SICD VCEP. It has been classified Pathogenic on ClinVar (225196).
PP3		✖	REVEL score of 0.727 predicts a deleterious effect. Not considered for this gene.

Curation History

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