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Variant: NM_000206.3(IL2RG):c.664C>T (p.Arg222Cys)

Version: 1.0

CA120885

10027 (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: 3f6af4f7-f617-4684-bd64-58811dc750eb
Approved on: 2024/1/17
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HGVS expressions

NM_000206.3:c.664C>T
NM_000206.3(IL2RG):c.664C>T (p.Arg222Cys)
NC_000023.11:g.71109321G>A
CM000685.2:g.71109321G>A
NC_000023.10:g.70329171G>A
CM000685.1:g.70329171G>A
NC_000023.9:g.70245896G>A
NG_009088.1:g.7233C>T
NG_021141.1:g.2468C>T
ENST00000482750.6:c.664C>T
ENST00000696903.1:n.715C>T
ENST00000374202.7:c.664C>T
ENST00000642473.1:n.1028C>T
ENST00000644022.1:n.930C>T
ENST00000644708.1:n.1070C>T
ENST00000644911.1:n.1070C>T
ENST00000645266.1:c.664C>T
ENST00000645518.1:c.664C>T
ENST00000646106.1:c.664C>T
ENST00000646505.1:c.664C>T
ENST00000647492.1:c.664C>T
ENST00000276110.6:n.1257C>T
ENST00000374188.7:c.-53C>T
ENST00000374202.6:c.664C>T
ENST00000456850.6:c.94C>T
ENST00000464642.5:c.532C>T
ENST00000482750.5:c.77C>T
ENST00000512747.3:n.591C>T
NM_000206.2:c.664C>T

Pathogenic

Met criteria codes 4

PP1_Strong PS4 PM2_Supporting PP4_Moderate

Not Met criteria codes 2

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

PS3 PP3

Evidence Links 0

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.664C>T (p.Arg222Cys) missense variant has been reported in several (atypical) SCID cases, including male (0.5pt) patient P1 (PMID: 29948574) in whom the variant was detected by WES (1pt) and there was a family history of SCID (first-degree male relatives from the maternal side with suspected primary immune deficiency, who were not available for this study; 0.5pt), additionally STAT5 phosphorylation after exposure to IL-2 was virtually absent in CD4 and CD8 T cells (1pt); together these are highly specific for SCID due to gamma chain deficiency (3pt; PP4_moderate). There are 5 genotype/phenotype positive individuals in the pedigree through 11 segregations of this variant (PMID: 29948574); P1 plus four second cousins are all hemizygous for this variant and affected with atypical SCID and an additional great uncle was also affected but not available for genotyping (5+ segregations; PP1_Strong). At least 15 additional male X-SCID patients have been reported (PMIDs: 25042067, 16227049, 10794431, 7557965) with this hemizygous variant (total 11pt; PS4) and this variant is absent from gnomADv2.1.1 (PM2_Supporting). 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, Pp1_Strong, PP4_Moderate and PM2_supporting. (VCEP specifications version 1).

Met criteria codes

PP1_Strong	✔	There are 5 genotype/phenotype positive individuals in the pedigree through 11 segregations of this variant (PMID: 29948574). P1 plus four second cousins are all hemizygous for this variant and affected with atypical SCID. An additional great uncle was also affected but not available for genotyping. (5+ segregations; PP1_Strong).
PS4	✔	At least 15 additional male X-SCID patients have been reported (PMIDs: 25042067, 16227049, 10794431, 7557965) with this hemizygous variant (total 11pt; PS4).
PM2_Supporting	✔	This variant is absent from gnomADv2.1.1 (PM2_Supporting).
PP4_Moderate	✔	For P1 (PMID: 29948574) male 0.5pt, WES 1pt, family history of SCID (first-degree male relatives from the maternal side with suspected primary immune deficiency, who were not available for this study) 0.5pt, STAT5 phosphorylation after exposure to IL-2 was virtually absent in CD4 and CD8 T cells 1pt (total 3pt; PP4_moderate)

Not Met criteria codes

PS3	✖	cDNA for a normal IL-2Rb chain was cotransfected into COS cells with either a normal IL-2Rg cDNA or the mutated version derived from the patient. A clear difference between the contribution of the patient and normal IL-2Rg chains was evident. Although appreciably greater IL-2 binding was observed to the combined b and g (R222C) chains, than to b alone, it was significantly lower than IL-2 binding to the normal bg complex. In summary, these results indicate that although receptors containing the mutated gamma chain are capable of binding IL-2, their affinity is reduced. Additionally, when cotransfected with Jak3 and the level of Jak3 phosphorylation induced by low

levels of IL-2 examined R222C was clearly less effective in modulating Jak3 activation. (PS3_NotMet) The SCID-VCEP has not approved functional studies in cell lines as evidence for assessing the pathogenicity of IL2RG.

PP3 ✖ REVEL score of 0.784 predicts a deleterious effect. Not considered for this gene.

Curation History

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