Variant: NM_000330.4(RS1):c.37C>T (p.Leu13Phe)

Version: 1.1

CA10360833

1421996 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: c3c89ae3-ff1a-435f-bb0e-e4e0f31ec5e8
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HGVS expressions

NM_000330.4:c.37C>T
NM_000330.4(RS1):c.37C>T (p.Leu13Phe)
NC_000023.11:g.18672032G>A
CM000685.2:g.18672032G>A
NC_000023.10:g.18690152G>A
CM000685.1:g.18690152G>A
NC_000023.9:g.18600073G>A
NG_008659.3:g.10417C>T
ENST00000379984.4:c.37C>T
ENST00000379984.3:c.37C>T
NM_000330.3:c.37C>T

Uncertain Significance

Not Met criteria codes 8

PM2 PM5 BS1 BS3 BP4 PS3 PS4 PP3

Evidence Links 0

Expert Panel

X-linked Inherited Retinal Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

X-linked Inherited Retinal Disease VCEP

NM_000330.4(RS1):c.37C>T (p.Leu13Phe) is a missense variant encoding the substitution of leucine with phenylalanine at amino acid 13. Another missense variant in the same codon, NM_000330.4(RS1):c.38T>C (p.Leu13Pro), has been reported in association with X-linked retinoschisis (PMID: 10533068, PMID: 20809529, PMID: 30652005), but has a higher Grantham score (98) than the present variant (22), so PM5 is not met. This variant is present in gnomAD v4.1.0 at a frequency of 0.00001010 among hemizygous individuals, with 4 variant alleles / 396,100 total hemizygous alleles, which is higher than the ClinGen X-linked IRD VCEP PM2_Supporting threshold of <0.000002 but lower than the BS1 threshold of >0.00002, so neither population code is met. This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 20809529), however, PS4_Supporting requires at least 2

unrelated probands, so this criterion was not met. The computational predictor REVEL gives a score of 0.444, which is lower than the ClinGen X-linked IRD VCEP PP3 threshold of >0.664 and higher than the BP4 threshold of<0.290 and does not predict a damaging effect on RS1 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.01, which is below the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. COS7 cells exogenously expressing the variant exhibit RS1 expression and secretion into the medium at levels similar to the wild-type control (PMID: 20809529). However, the BS3_Supporting code is considered not applicable for RS1 variants due to the absence of sufficient benign control variants from established assays of RS1 function. In summary, this variant is classified as a variant of uncertain significance for X-linked retinoschisis based on the ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0: None.

Not Met criteria codes

PM2	✖	This variant is present in gnomAD v4.1.0 at a frequency of 0.00001010 among hemizygous individuals, with 4 variant alleles / 396,100 total hemizygous alleles, which is higher than the ClinGen X-linked IRD VCEP PM2_Supporting threshold of <0.000002 but lower than the BS1 threshold of >0.00002, which fails to meet these criteria.
PM5	✖	Another missense variant in the same codon, NM_000330.4(RS1):c.38T>C (p.Leu13Pro), has been reported in association with X-linked retinoschisis (PMID: 10533068, PMID: 20809529, PMID: 30652005), but has a higher Grantham score (98) than the present variant (22), so PM5 is not met.
BS1	✖	This variant is present in gnomAD v.4.1.0 at a frequency of 0.00001010 among hemizygous individuals, with 4 variant alleles / 396100 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2_Supporting and BS1 threshold of 0.000002 to 0.00002 and fails to meet these criteria.
BS3	✖	COS7 cells exogenously expressing the variant exhibit RS1 expression and secretion into the medium similar to the wild-type control (PMID: 20809529). However, the BS3_Supporting code is considered not applicable for RS1 variants due to the absence of sufficient benign control variants from established assays of RS1 function.
BP4	✖	The computational predictor REVEL gives a score of 0.444, which is between the ClinGen X-linked IRD VCEP threshold of 0.664 to 0.290 and does not predict a damaging effect on RS1 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.01, which is below the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. Collectively, both BP4 and PP3 codes do not apply.
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	✖	This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with XLRS (PMID: 20809529). PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met.
PP3	✖	The computational predictor REVEL gives a score of 0.444, which is between the ClinGen X-linked IRD VCEP threshold of 0.664 to 0.290 and does not predict a damaging effect on RS1 function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.01, which is below the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. Collectively, both BP4 and PP3 codes do not apply.

Curation History

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