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Variant: NM_003159.3:c.2714-1476G>T

Version: 1.0

CA412371862

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 87406abb-43dc-40c9-8538-4db5f8593da9
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HGVS expressions

NM_003159.3:c.2714-1476G>T
NC_000023.11:g.18644531G>T
CM000685.2:g.18644531G>T
NC_000023.10:g.18662651G>T
CM000685.1:g.18662651G>T
NC_000023.9:g.18572572G>T
NG_008475.1:g.223927G>T
NG_008659.3:g.37918C>A
ENST00000379984.4:c.421C>A
ENST00000379984.3:c.421C>A
ENST00000379989.6:c.2714-1476G>T
ENST00000379996.7:c.2714-1476G>T
ENST00000476595.1:n.912C>A
NM_000330.3:c.421C>A
NM_001037343.1:c.2714-1476G>T
NM_003159.2:c.2714-1476G>T
NM_000330.4:c.421C>A
NM_001037343.2:c.2714-1476G>T

Likely Pathogenic

Met criteria codes 6

PM5 PP3 PP4 PM2_Supporting PS4_Supporting PS3_Supporting

Evidence Links 1

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.421C>A (p.Arg141Ser) is a missense variant encoding the substitution of arginine with serine at amino acid 141. Another missense variant in the same codon, NM_000330.4(RS1):c.422G>A (p.Arg141His), (PMID: 29851975, PMID: 34645606, PMID: 30450322, PMID: 29739629, PMID: 35984651, PMID: 30652005, PMID: 19093009, PMID: 30630865, PMID: 30040949, PMID: 17525175, PMID: 30630865, PMID: 30040949) has been classified as pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (110) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype of the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 29851975, PP4). This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis, as well as a second apparently unrelated proband previously used for the PP4 code (PMID: 34645606, PS4_Supporting). The computational predictor REVEL gives a score of 0.765, which is within the ClinGen X-linked IRD VCEP range between 0.772 to 0.644 and predicts a damaging effect on RS1 function (PP3). The computational splicing predictor SpliceAI gives a delta score of 0.02 for acceptor loss, which is below the ClinGen X linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing. Carbohydrate-agarose affinity chromatography assays of wild-type and variant RS1 secreted from Weri-Rb1 cells showed reduced binding to galactose-agarose by RS1 harboring the variant relative to the wild-type control (PS3_Supporting, PMID: 18690710). In summary, this variant is classified as likely pathogenic 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: PM2_Supporting, PP3, PS3_Supporting, PP4, PS4_Supporting, and PM5.

Met criteria codes

PM5	✔	Another missense variant in the same codon, [c.422G>A, p. Arg141His], (PMID: 19093009) has been classified as pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance than the comparison variant, and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
PP3	✔	The computational predictor REVEL gives a score of [0.765], which is within the ClinGen X-linked IRD VCEP range between 0.772 to 0.644 and predicts a damaging effect on RS1 function (PP3). The computational splicing predictor SpliceAI gives a delta score of [0.02] for [acceptor loss], which is below the ClinGen X linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing.
PP4	✔	At least one proband harboring this variant exhibits a phenotype of the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 29851975, PP4).
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: PMID: 34645606, PS4_Supporting).
PS3_Supporting	✔	Carbohydrate-agarose affinity chromatography assays of wild-type and variant RS1 secreted from Weri-Rb1 cells showed reduced binding to galactose-agarose by RS1 harboring the variant relative to the wild-type control (PS3_Supporting, PMID: 18690710). Dyka et al. showed reduced binding of the RS1 to galactose-agarose than WT. PubMed:18690710

Curation History

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