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Variant: NM_025114.4(CEP290):c.2414T>C (p.Leu805Pro)

Version: 1.0

CA6712335

866922 (ClinVar)

Gene: CEP290 (HGNC:80184)
Condition: CEP290-related ciliopathy (MONDO:0100451)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8853a8cb-6125-497d-bafa-adfccd503e4d
Approved on: 2026/7/20
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HGVS expressions

NM_025114.4:c.2414T>C
NM_025114.4(CEP290):c.2414T>C (p.Leu805Pro)
NC_000012.12:g.88109135A>G
CM000674.2:g.88109135A>G
NC_000012.11:g.88502912A>G
CM000674.1:g.88502912A>G
NC_000012.10:g.87027043A>G
NG_008417.1:g.38082T>C
NG_008417.2:g.38082T>C
ENST00000309041.12:c.2414T>C
ENST00000552810.6:c.2414T>C
ENST00000672414.2:c.*585T>C
ENST00000673058.2:c.2414T>C
ENST00000674971.1:c.2414T>C
ENST00000675230.1:c.2393T>C
ENST00000675408.1:c.2414T>C
ENST00000675476.1:c.3275T>C
ENST00000675628.1:n.2641T>C
ENST00000675794.1:c.*585T>C
ENST00000675833.1:c.3182T>C
ENST00000676074.1:c.2414T>C
ENST00000676363.1:n.4477T>C
ENST00000676448.1:c.*327T>C
ENST00000309041.11:c.2420T>C
ENST00000397838.7:c.2418T>C
ENST00000552810.5:c.2414T>C
ENST00000604024.5:c.1673T>C
NM_025114.3:c.2414T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP1 PP3 PP4 PM3_Strong

Evidence Links 0

Expert Panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CEP290 Version 1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

NM_025114.4(CEP290):c.2414T>C (p.Leu805Pro) is a missense variant that replaces the leucine with proline at amino acid 805. This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.0000143, with 21 alleles / 1,464,678 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting). The computational predictor CADD gives a score of 26.5, which is above the ClinGen LCA/eoRD VCEP threshold of ≥25.3 and predicts a damaging effect on CEP290 protein function (PP3). This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_025114.4(CEP290):c.1666del (p.Ile556fs) variant or the NM_025114.4(CEP290):c.4452_4455del (p.Lys1484AsnfsTer4) variant confirmed in trans, which were previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). At least one proband harboring this variant exhibits a phenotype including diagnosis of cone-rod dystrophy (0.5 pts) with onset at birth (0.5 pts), frequent rubbing of the eyes (0.5 pts), glare sensitivity (0.5 pts), poor visual acuity (0.5 pts), visual field constriction (0.5 pts), normal scotopic but absent photopic electroretinogram responses, and a color vision disorder, with genotyping by whole genome sequencing and inherited retinal disease gene panel that did not identify an alternative basis for retinal disease (4 pts), which together are specific for CEP290-related ciliopathy (total 7 points, PMID: 37642804, PP4). The variant has also been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PMID: 28559085, PP1). In summary, this variant meets the criteria to be classified as Likely Pathogenic for CEP290-related ciliopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2_Supporting, PP3, PM3_Strong, PP4, and PP1. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

PM2_Supporting	✔	This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.0000143, with 21 alleles / 1,464,678 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the compound heterozygous state (PMID: 28559085, PP1).
PP3	✔	The computational predictor CADD gives a score of 26.5, which is above the ClinGen LCA/eoRD VCEP threshold of ≥25.3 and predicts a damaging effect on CEP290 protein function (PP3).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of cone-rod dystrophy (0.5 pts) with onset at birth (0.5 pts), frequent rubbing of the eyes (0.5 pts), glare sensitivity (0.5 pts), poor visual acuity (0.5 pts), visual field constriction (0.5 pts), normal scotopic but absent photopic electroretinogram responses, and a color vision disorder, with genotyping by whole genome sequencing and inherited retinal disease gene panel that did not identify an alternative basis for retinal disease (4 pts), which together are specific for RPE65-related recessive retinopathy (total 7 points, PMID: 37642804, PP4).
PM3_Strong	✔	This variant has been reported in at least 2 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_025114.4(CEP290):c.1666del (p.Ile556fs) variant or the

NM_025114.4(CEP290):c.4452_4455del (p.Lys1484AsnfsTer4) variant confirmed in trans, which were previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong). This variant has been reported in 3 additional affected patients with either the c.5493del, p.Ala1832Profs*19, c.1065+1G>A, or c.4962_4963del, p.(Glu1656Asnfs*3) variant suspected in trans (VCEP member-provided data). These have not been included in PM3 pending confirmation of necessary phenotype details.

Curation History

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