

Variant: NM_025114.4(CEP290):c.1466T>C (p.Leu489Pro)

Version: 1.0

CA385979889 [↗](#)

2932624 (ClinVar) [↗](#)

Gene: CEP290 ([HGNC:80184](#))

Condition: CEP290-related ciliopathy ([MONDO:0100451](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 57abb096-4a3b-4e54-b774-0e897a8bd09d

Approved on: 2026/7/20

Published on: 2026/7/20

HGVS expressions

NM_025114.4(CEP290):c.1466T>C (p.Leu489Pro)

NM_025114.4:c.1466T>C

NC_000012.12:g.88120170A>G

CM000674.2:g.88120170A>G

NC_000012.11:g.88513947A>G

CM000674.1:g.88513947A>G

NC_000012.10:g.87038078A>G

NG_008417.1:g.27047T>C

NG_008417.2:g.27047T>C

ENST00000309041.12:c.1466T>C

ENST00000397838.8:c.1412T>C

ENST00000547926.7:c.1466T>C

ENST00000552810.6:c.1466T>C

ENST00000671822.2:n.1693T>C

ENST00000672414.2:c.1466T>C

ENST00000673058.2:c.1466T>C

ENST00000674971.1:c.1466T>C

ENST00000675230.1:c.1445T>C

ENST00000675408.1:c.1466T>C

ENST00000675476.1:c.1466T>C

ENST00000675559.1:c.1466T>C

ENST00000675628.1:n.1693T>C

ENST00000675794.1:c.1466T>C

ENST00000675833.1:c.1466T>C

ENST00000676074.1:c.1466T>C

ENST00000676351.1:c.*979T>C

ENST00000676363.1:n.3529T>C

ENST00000676418.1:c.1466T>C

ENST00000676448.1:c.1466T>C

ENST00000309041.11:c.1466T>C

ENST00000397838.7:c.1466T>C

ENST00000547926.6:c.1364T>C

ENST00000552810.5:c.1466T>C

ENST00000604024.5:c.632T>C

NM_025114.3:c.1466T>C

Uncertain Significance

Met criteria codes 4

PP1PP3PM3PM2_Supporting

Not Met criteria codes 1

PP4

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.1466T>C (p.Leu489Pro) is a missense variant that replaces leucine with proline at amino acid 489. This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.0000006505, with 1 allele / 1,537,272 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_025114.4(CEP290):c.1666del (p.Ile556fs) variant confirmed in trans, which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PMID: 34196655, PM3). The proband exhibits a phenotype including diagnosis of either Leber congenital amaurosis, early onset severe retinal dystrophy, or retinitis pigmentosa (0.5 pts), which is not sufficiently specific for CEP290-related ciliopathy to meet the PP4 code (0.5 total points, PMID: 34196655). 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: 34196655, PP1). 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). Additionally, the splicing impact predictor SpliceAI gives a score of 0.01 for donor loss, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing. In summary, this variant meets the criteria to be classified as a Variant of Uncertain Significance for CEP290-related ciliopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2_Supporting, PM3, PP3, and PP1. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes			
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: 34196655, 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). Additionally, the splicing impact predictor SpliceAI gives a score of 0.01 for donor loss, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.
PM3			This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_025114.4(CEP290):c.1666del (p.Ile556fs) variant confirmed in trans, which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PMID: 34196655, PM3).
PM2_Supporting			This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.0000006505, with 1 allele / 1,537,272 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting).

Not Met criteria codes

PP4



At least one proband harboring this variant exhibits a phenotype including diagnosis of either Leber congenital amaurosis, early onset severe retinal dystrophy, or retinitis pigmentosa (0.5 pts), which is not sufficiently specific for CEP290-related ciliopathy to meet the PP4 code (0.5 total points, PMID: 34196655).

Curation History

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