The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_025114.4(CEP290):c.148C>T (p.His50Tyr)

Version: 1.0

CA10581687

236469 (ClinVar)

Gene: CEP290 (HGNC:80184)
Condition: CEP290-related ciliopathy (MONDO:0100451)
Inheritance Mode: Autosomal recessive inheritance
UUID: a3fb4056-958f-4d2d-a567-0290d42c1e94
Approved on: 2026/7/20
Published on: 2026/7/20

HGVS expressions

NM_025114.4(CEP290):c.148C>T (p.His50Tyr)
NM_025114.4:c.148C>T
NC_000012.12:g.88140988G>A
CM000674.2:g.88140988G>A
NC_000012.11:g.88534765G>A
CM000674.1:g.88534765G>A
NC_000012.10:g.87058896G>A
NG_008417.1:g.6229C>T
NG_021187.1:g.3693G>A
NG_008417.2:g.6229C>T
ENST00000309041.12:c.148C>T
ENST00000397838.8:c.148C>T
ENST00000547926.7:c.148C>T
ENST00000550962.6:c.148C>T
ENST00000552770.3:c.148C>T
ENST00000552810.6:c.148C>T
ENST00000671822.2:n.375C>T
ENST00000672414.2:c.148C>T
ENST00000673058.2:c.148C>T
ENST00000674971.1:c.148C>T
ENST00000675230.1:c.148C>T
ENST00000675361.1:c.148C>T
ENST00000675408.1:c.148C>T
ENST00000675476.1:c.148C>T
ENST00000675559.1:c.148C>T
ENST00000675628.1:n.375C>T
ENST00000675794.1:c.148C>T
ENST00000675833.1:c.148C>T
ENST00000676074.1:c.148C>T
ENST00000676331.1:n.375C>T
ENST00000676351.1:c.148C>T
ENST00000676418.1:c.148C>T
ENST00000676448.1:c.148C>T
ENST00000309041.11:c.148C>T
ENST00000397838.7:c.148C>T
ENST00000547926.6:c.46C>T
ENST00000550962.5:c.148C>T

ENST00000552770.2:c.7C>T
ENST00000552810.5:c.148C>T
NM_025114.3:c.148C>T

Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4 PP1_Strong 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.148C>T (p.His50Tyr) is a missense variant that replaces histidine with tyrosine at amino acid 50. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMIDs: 29398085, 28418496). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the NM_025114.4(CEP290):c.4393C>T (p.Arg1465Ter) variant confirmed in trans (1 point, PMID: 29398085), which was 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 a diagnosis of Leber congenital amaurosis (0.5 pts), symptoms present from birth (0.5 pts), severely reduced visual acuity (0.5 pts), no clear progression in first decade (0.5 pts), vision that was worse under bright light (0.5 pts), impaired night vision (0.5 pts), fundi showing widespread outer retinal atrophy with relative sparing of the macula (1 pt), and optical coherence tomography showed only a small region of preservation of the photoreceptor layers, which together are specific for CEP290-related ciliopathy (total 4 points, PMID: 29398085 and additional details from coauthor, PP4). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus at least 4 similarly affected relatives, with the variant present in the compound heterozygous state (PMID:29298085), and in a family with 3 homozygous siblings (PMID:28418496, PP1_Strong). The computational predictor CADD gives a score of 25.9, 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 0.08, 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 Pathogenic for CEP290-related ciliopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2_Supporting, PM3_Strong, PP4, PP1_Strong, and PP3. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3	✔	The computational predictor CADD gives a score of 25.9, which is above the ClinGen LCA/eoRD VCEP threshold of ≥25.3 and predicts a damaging effect on CEP290 protein function (PP3). The splicing impact predictor SpliceAI gives a score of 0.08 for acceptor loss, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not predict a deleterious impact on splicing.

PP4		✔	At least one proband harboring this variant exhibits a phenotype including a diagnosis of LCA (0.5 pts), symptoms present from birth (0.5 pts), severely reduced visual acuity (0.5 pts) and no clear progression in first decade (0.5 pts). Vision was worse under bright light (0.5 pts), night vision always impaired (0.5 pts). Fundi showed widespread outer retinal atrophy with relative sparing of the macula (1 pt). OCT showed only a small region of preservation of the photoreceptor layers. Together these are specific for CEP290-related ciliopathy (total 4 points, PMID: 29398085 and additional details from coauthor, PP4).
PP1_Strong		✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus at least 4 similarly affected relatives, with the variant present in the compound heterozygous state (PMID:29298085) and in a family with 3 homozygous siblings (PMID:28418496) (PP1_Strong).
PM3_Strong		✔	This variant has been reported in at least 2 unrelated probands with early-onset severe retinal dystrophy who were homozygous for the variant (1 point, PMIDs: 29398085, 28418496). This variant has also been reported in at least 1 proband with early-onset severe retinal dystrophy who was compound heterozygous with the p.Arg1465Ter variant confirmed in trans (1 point, PMID: 29398085), which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (2 total points, PM3_Strong).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.