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Variant: NM_025114.4(CEP290):c.185A>G (p.Lys62Arg)

Version: 1.0

CA385989473

3896422 (ClinVar)

Gene: CEP290 (HGNC:80184)
Condition: CEP290-related ciliopathy (MONDO:0100451)
Inheritance Mode: Autosomal recessive inheritance
UUID: c234605c-b269-4128-92aa-a1c8e378c8e8
Approved on: 2026/7/20
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HGVS expressions

NM_025114.4:c.185A>G
NM_025114.4(CEP290):c.185A>G (p.Lys62Arg)
NC_000012.12:g.88139560T>C
CM000674.2:g.88139560T>C
NC_000012.11:g.88533337T>C
CM000674.1:g.88533337T>C
NC_000012.10:g.87057468T>C
NG_008417.1:g.7657A>G
NG_021187.1:g.2265T>C
NG_008417.2:g.7657A>G
ENST00000309041.12:c.185A>G
ENST00000397838.8:c.185A>G
ENST00000547926.7:c.185A>G
ENST00000550962.6:c.185A>G
ENST00000552770.3:c.185A>G
ENST00000552810.6:c.185A>G
ENST00000671822.2:n.412A>G
ENST00000672414.2:c.185A>G
ENST00000673058.2:c.185A>G
ENST00000674971.1:c.185A>G
ENST00000675230.1:c.185A>G
ENST00000675361.1:c.185A>G
ENST00000675408.1:c.185A>G
ENST00000675476.1:c.185A>G
ENST00000675559.1:c.185A>G
ENST00000675628.1:n.412A>G
ENST00000675794.1:c.185A>G
ENST00000675833.1:c.185A>G
ENST00000676074.1:c.185A>G
ENST00000676331.1:n.412A>G
ENST00000676351.1:c.185A>G
ENST00000676418.1:c.185A>G
ENST00000676448.1:c.185A>G
ENST00000309041.11:c.185A>G
ENST00000397838.7:c.185A>G
ENST00000547926.6:c.83A>G
ENST00000550962.5:c.185A>G

ENST00000552770.2:c.44A>G
ENST00000552810.5:c.185A>G
NM_025114.3:c.185A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PP4_Moderate PM2_Supporting

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.185A>G (p.Lys62Arg) is a missense substitution replacing lysine with arginine at amino acid 62. This variant is absent from gnomAD v4.1.1 (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.2991+1655A>G variant confirmed in trans, which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PMID: 34321860, PM3). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset before age 1 year (0.5 pts), and genotyping by next-generation sequencing that did not identify an alternative basis for retinal disease (2 pts), which together are not sufficiently specific for CEP290-related ciliopathy to meet the PP4 code (total 3 points, PMID: 34321860). A VCEP member has provided a more detailed clinical phenotype of the patient (11 points, VCEP member-provided data, PP4_Moderate). The computational predictor CADD gives a PHRED score of 26.4, 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 0.00, 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 Likely Pathogenic for CEP290-related ciliopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2_Supporting, PM3, PP4_Moderate, and PP3. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

PP3	✔	The computational predictor CADD gives a PHRED score of 26.4, 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 0.00, 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.2991+1655A>G variant confirmed in trans, which was previously classified pathogenic by the ClinGen LCA/eoRD VCEP (1 total point, PMID: 34321860, PM3).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts) with onset before age 1 year (0.5 pts), and genotyping by next-generation sequencing that did not identify

an alternative basis for retinal disease (2 pts), which together are not sufficiently specific for CEP290-related ciliopathy to meet the PP4 code (total 3 points, PMID: 34321860). A second unpublished report provided by a VCEP member included a more detailed clinical phenotype (11 points, VCEP member-provided data, PP4_Moderate).

PM2_Supporting ✔ This variant is absent from gnomAD v4.1.1 (PM2_Supporting).

Curation History

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