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.223A>G (p.Lys75Glu)

Version: 1.0

CA6712876

802880 (ClinVar)

Gene: CEP290 (HGNC:80184)
Condition: CEP290-related ciliopathy (MONDO:0100451)
Inheritance Mode: Autosomal recessive inheritance
UUID: 409ddea2-bc87-440b-9b4c-80f00c8b00ba
Approved on: 2026/7/20
Published on: 2026/7/20

HGVS expressions

NM_025114.4(CEP290):c.223A>G (p.Lys75Glu)
NM_025114.4:c.223A>G
NC_000012.12:g.88139522T>C
CM000674.2:g.88139522T>C
NC_000012.11:g.88533299T>C
CM000674.1:g.88533299T>C
NC_000012.10:g.87057430T>C
NG_008417.1:g.7695A>G
NG_021187.1:g.2227T>C
NG_008417.2:g.7695A>G
ENST00000309041.12:c.223A>G
ENST00000397838.8:c.223A>G
ENST00000547926.7:c.223A>G
ENST00000550962.6:c.223A>G
ENST00000552770.3:c.223A>G
ENST00000552810.6:c.223A>G
ENST00000671822.2:n.450A>G
ENST00000672414.2:c.223A>G
ENST00000673058.2:c.223A>G
ENST00000674971.1:c.223A>G
ENST00000675230.1:c.223A>G
ENST00000675361.1:c.223A>G
ENST00000675408.1:c.223A>G
ENST00000675476.1:c.223A>G
ENST00000675559.1:c.223A>G
ENST00000675628.1:n.450A>G
ENST00000675794.1:c.223A>G
ENST00000675833.1:c.223A>G
ENST00000676074.1:c.223A>G
ENST00000676331.1:n.450A>G
ENST00000676351.1:c.223A>G
ENST00000676418.1:c.223A>G
ENST00000676448.1:c.223A>G
ENST00000309041.11:c.223A>G
ENST00000397838.7:c.223A>G
ENST00000547926.6:c.121A>G
ENST00000550962.5:c.223A>G

ENST00000552770.2:c.82A>G
ENST00000552810.5:c.223A>G
NM_025114.3:c.223A>G

Likely Pathogenic

Met criteria codes 3

PM3_Strong | PM2_Supporting | PP4

Not Met criteria codes 2

BP4 | PP3

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.223A>G (p.Lys75Glu) is a missense variant that replaces lysine with glutamic acid at amino acid 75. This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.00001501, with 24 alleles / 1,598,538 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 homozygous for the variant (0.5 points, PMID: 36909829). This variant has also been reported in at least 3 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_025114.4(CEP290):c.1984C>T (p.Gln662Ter) variant confirmed in trans (1 point, PMID: 34321860), the NM_025114.4(CEP290):c.1347dup (p.Asp450fs) variant confirmed in trans (1 point, VCEP member-provided data), or the NM_025114.4(CEP290):c.1753C>T (p.Gln585Ter) variant suspected in trans (0.5 points, VCEP member-provided data), which were previously classified pathogenic or likely pathogenic by the ClinGen LCA/eoRD VCEP (3 total points, PM3_Strong). This variant has been reported in two additional patients diagnosed with retinitis pigmentosa in adolescence or adulthood with no available details regarding onset with either the NM_025114.4(CEP290):c.254dup (p.Asn85fs) variant or the NM_025114.4(CEP290):c.1347dup (p.Asp450fs) variant suspected in trans. These have not been included in PM3 pending confirmation of necessary phenotype details. At least one proband harboring this variant exhibits a phenotype including diagnosis of retinitis pigmentosa with onset in infancy / childhood (0.5 pts), nyctalopia (0.5 pts) and moderate myopia, with genotyping by whole exome sequencing that did not identify an alternative basis for retinal disease (4 pts), which together are specific for CEP290-related ciliopathy (5 total points, PMID: 36909829, PP4). The computational predictor CADD gives a score of 23.8, which is below the ClinGen LCA/eoRD VCEP threshold of ≥25.3 and does not predict a damaging effect on CEP290 protein function. Additionally, 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_Strong, and PP4. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

PM3_Strong	✔	This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 points, PMID: 36909829). This variant has also been reported in at least 3 probands with early-onset severe retinal dystrophy who were compound heterozygous with either the NM_025114.4(CEP290):c.1984C>T (p.Gln662Ter) variant confirmed in trans (1 point, PMID: 34321860), the NM_025114.4(CEP290):c.1347dup (p.Asp450fs) variant confirmed in trans (1 point, VCEP member-provided data), or the

NM_025114.4(CEP290):c.1753C>T (p.Gln585Ter) variant suspected in trans (0.5 points, VCEP member-provided data), which were previously classified pathogenic or likely pathogenic by the ClinGen LCA/eoRD VCEP (3 total points, PM3_Strong). This variant has been reported in two additional patients diagnosed with retinitis pigmentosa in adolescence or adulthood with no available details regarding onset with either the NM_025114.4(CEP290):c.254dup (p.Asn85fs) variant or the NM_025114.4(CEP290):c.1347dup (p.Asp450fs) variant suspected in trans. These have not been included in PM3 pending confirmation of necessary phenotype details.

PM2_Supporting	✔	This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.00001501, with 24 alleles / 1.598.538 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of retinitis pigmentosa with onset in infancy / childhood (0.5 pts), nyctalopia (0.5 pts), visual acuity 1.0/1.0, and moderate myopia, with genotyping by whole exome sequencing that did not identify an alternative basis for retinal disease (4 pts), which together are specific for CEP290-related ciliopathy (5 total points, PMID: 36909829, PP4).

Not Met criteria codes

BP4	✖	The computational predictor CADD gives a score of 23.8, which is above the ClinGen LCA/eoRD VCEP threshold of <17.3 and does not predict a non-damaging effect on CEP290 protein function.
PP3	✖	The computational predictor CADD gives a score of 23.8, which is below the ClinGen LCA/eoRD VCEP threshold of ≥25.3 and does not predict a damaging effect on CEP290 protein function. Additionally, the splicing impact predictor SpliceAI gives a score of 0.0, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≥0.2 and does not strongly predict an impact on splicing.

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_025114.4(CEP290):c.223A>G (p.Ly…	Likely Pathogenic	CEP290-Related Ciliopathy	2026-07-20	1.0	ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CEP290 Version 1.0	CEP290

Showing 1 to 1 of 1 rows

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