

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

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HGVS expressions

NM_025114.4:c.223A>G

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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

PM2_Supporting PM3_Strong 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

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).

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.

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 [↗](#)

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