

Variant: NM_025114.4(CEP290):c.5998A>G (p.Ile2000Val)

Version: 1.0

CA6711610 [↗](#)

281249 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c6bead1b-4767-4da6-9897-aef4e49f0777

Approved on: 2026/7/20

Published on: 2026/7/20

HGVS expressions

NM_025114.4:c.5998A>G

NM_025114.4(CEP290):c.5998A>G (p.Ile2000Val)

NC_000012.12:g.88071307T>C

CM000674.2:g.88071307T>C

NC_000012.11:g.88465084T>C

CM000674.1:g.88465084T>C

NC_000012.10:g.86989215T>C

NG_008417.1:g.75910A>G

NG_008417.2:g.75910A>G

ENST00000309041.12:c.5998A>G

ENST00000547691.8:c.3282A>G

ENST00000552810.6:c.5998A>G

ENST00000672414.2:c.*4169A>G

ENST00000672647.1:n.4358A>G

ENST00000673058.2:c.5998A>G

ENST00000674971.1:c.5998A>G

ENST00000675230.1:c.5977A>G

ENST00000675408.1:c.5998A>G

ENST00000675476.1:c.6859A>G

ENST00000675628.1:n.6225A>G

ENST00000675794.1:c.*4169A>G

ENST00000675833.1:c.6766A>G

ENST00000675894.1:n.2303A>G

ENST00000676074.1:c.5998A>G

ENST00000676181.1:n.4926A>G

ENST00000676363.1:n.11724A>G

ENST00000676448.1:c.*3911A>G

ENST00000309041.11:c.6004A>G

ENST00000547691.6:c.3178A>G

ENST00000552810.5:c.5998A>G

NM_025114.3:c.5998A>G

Met criteria codes **2**

Uncertain Significance

BP4

PM2_Supporting

Expert Panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP [↗](#)

Not Met criteria codes 3

BS1 BP5 PM3

Evidence Links 0

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.5998A>G (p.Ile2000Val) is a missense variant that replaces isoleucine with valine at amino acid 2000. This variant is present in gnomAD v4.1.1 at a Grpmax allele frequency of 0.001149, with 12 alleles / 6,020 total alleles in the Middle Eastern population, which is lower than the ClinGen LCA/eoRD VCEP BS1 threshold of >0.0016. This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.0001209, with 194 alleles / 1,604,948 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 renal anomalies and renal disease who harbored the variant in the compound heterozygous state, however, the proband was not counted for PM3 because sufficient phenotype details were not reported and because the NM_025114.4(CEP290):c.963T>A (p.Asp321Glu) variant suspected in trans has been classified as a VUS (PMID: 40718208). The variant has also been reported in at least 1 proband with a severe sperm motility disorder who harbored the variant in the compound heterozygous state, however, the proband was not counted for PM3 because sufficient details were not reported and because the NM_025114.4(CEP290):c.1092T>G (p.Ile364Met) variant suspected in trans has been classified as likely benign. The proband also harbored homozygous missense variants in several other candidate genes, but was not counted for BP5 because sufficient phenotype details were not reported and because this code is considered not applicable to CEP290 due to the high genetic heterogeneity and limited phenotypic specificities of retinal dystrophies (PMID: 34089056). The computational predictor CADD gives a PHRED score of 12.9, which is below the ClinGen LCA/eoRD VCEP threshold of <17.3 and predicts a non-damaging effect on CEP290 protein function. In addition, the splicing impact predictor SpliceAI gives a delta score of 0.00 for all splicing events, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≤0.1 and does not predict an impact on splicing (BP4). 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 and BP4. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

BP4			The computational predictor CADD gives a PHRED score of 12.9, which is below the ClinGen LCA/eoRD VCEP threshold of <17.3 and predicts a non-damaging effect on CEP290 protein function. In addition, the splicing impact predictor SpliceAI gives a delta score of 0.00 for all splicing events, which is below the ClinGen LCA/eoRD VCEP recommended threshold of ≤0.1 and does not predict an impact on splicing (BP4).
PM2_Supporting			This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.0001209, with 194 alleles / 1,604,948 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting).

Not Met criteria codes

BS1			This variant is present in gnomAD v4.1.1 at a Grpmax allele frequency of 0.001149, with 12 alleles / 6,020 total alleles in the Middle Eastern population, which is lower than the ClinGen LCA/eoRD VCEP BS1 threshold of >0.0016.
BP5			

The variant has been reported in at least 1 proband with a severe sperm motility disorder who harbored the variant in the compound heterozygous state and also harbored homozygous missense variants in several other candidate genes, however, the proband was not counted for BP5 because sufficient phenotype details were not reported and because this code is considered not applicable to CEP290 due to the high genetic heterogeneity and limited phenotypic specificities of retinal dystrophies (PMID: 34089056).

PM3



This variant has been reported in at least 1 proband with renal anomalies and renal disease who harbored the variant in the compound heterozygous state, however, the proband was not counted for PM3 because sufficient phenotype details were not reported and because the NM_025114.4(CEP290):c.963T>A (p.Asp321Glu) variant suspected in trans has been classified as a VUS (PMID: 40718208). The variant has also been reported in at least 1 proband with a severe sperm motility disorder who harbored the variant in the compound heterozygous state, however, the proband was not counted for PM3 because sufficient details were not reported and because the NM_025114.4(CEP290):c.1092T>G (p.Ile364Met) variant suspected in trans has been classified as likely benign.

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.