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Variant: NM_025114.4(CEP290):c.4655AAG[2] (p.Glu1554del)

Version: 1.0

CA6711895

953502 (ClinVar)

Gene: CEP290 (HGNC:80184)
Condition: CEP290-related ciliopathy (MONDO:0100451)
Inheritance Mode: Autosomal recessive inheritance
UUID: f8e77c54-95ee-4095-88d7-22c8e317f59f
Approved on: 2026/7/20
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HGVS expressions

NM_025114.4(CEP290):c.4655AAG[2] (p.Glu1554del)
NM_025114.4:c.4655AAG[2]
NM_025114.4:c.4661_4663del
NC_000012.12:g.88084633_88084635del
CM000674.2:g.88084633_88084635del
NC_000012.11:g.88478410_88478412del
CM000674.1:g.88478410_88478412del
NC_000012.10:g.87002541_87002543del
NG_008417.1:g.62588_62590del
NG_008417.2:g.62588_62590del
ENST00000309041.12:c.4661_4663del
ENST00000547691.8:c.1945_1947del
ENST00000552810.6:c.4661_4663del
ENST00000672414.2:c.*2832_*2834del
ENST00000672647.1:n.3021_3023del
ENST00000673058.2:c.4661_4663del
ENST00000674971.1:c.4661_4663del
ENST00000675230.1:c.4640_4642del
ENST00000675408.1:c.4661_4663del
ENST00000675476.1:c.5522_5524del
ENST00000675628.1:n.4888_4890del
ENST00000675794.1:c.*2832_*2834del
ENST00000675833.1:c.5429_5431del
ENST00000675894.1:n.966_968del
ENST00000676074.1:c.4661_4663del
ENST00000676181.1:n.3589_3591del
ENST00000676363.1:n.10387_10389del
ENST00000676448.1:c.*2574_*2576del
ENST00000309041.11:c.4667_4669del
ENST00000547691.6:c.1841_1843del
ENST00000552810.5:c.4661_4663del
NM_025114.3:c.4661_4663del

Pathogenic

Met criteria codes 5

PP1_Moderate | PM3_Very Strong | PM4_Supporting | PP4 | PM2_Supporting

Not Met criteria codes 1

BP2

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.4661_4663del (p.Glu1554del) is an in-frame deletion causing a change in the length of the protein by 1 amino acid in a non-repeat region, with at least one of the deleted base pairs highly conserved with a PhyloP conservation score of 7.37 (PM4_Supporting). This variant is present in gnomAD v.4.1.1 at a total allele frequency of 0.00002232, with 36 alleles / 1,612,700 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: 29398085). This variant has also been reported in at least 5 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_025114.4(CEP290):c.4024C>T (p.Gln1342Ter) variant or the NM_025114.4(CEP290):c.5850del (p.Phe1950fs) variant suspected in trans (1 point, PMID: 33970760, PMID: 17345604) or with the NM_025114.4(CEP290):c.297+1G>T variant, the NM_025114.4(CEP290):c.3904C>T (p.Gln1302Ter) variant, or the NM_025114.4(CEP290):c.1219_1220del (p.Met407GlufsTer14) variant confirmed in trans (3 points, PMID: 28973549, PMID: 32165824, PMID: 34196655), which were previously classified pathogenic by the ClinGen LCA/eoRD VCEP (4.5 total points, PM3_VeryStrong). At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), onset before age 5 years (0.5 pts), extinguished electroretinogram responses from rods (0.5 pts) and cones (0.5 pts), central visual acuity limited to light perception (0.5 pts), white mottling in the peripheral pigmentation (0.5 pts), absence of vasculopathy / normal optic disc color, and decreased flash visual evoked potentials, with genotyping by next-generation sequencing identifying no alternative basis for retinal disease (2 pts), which together are specific for CEP290-related ciliopathy (total 5 points, PMID: 33970760, PP4). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PP1_Moderate; PMID: 29398085). 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: PM4_Supporting, PM2_Supporting, PM3_Very-Strong, PP1_Moderate, and PP4. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

PP1_Moderate	✔	The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 2 similarly affected relatives, with the variant present in the homozygous state (PP1_Moderate; PMID: 29398085).
PM3_Very 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: 29398085). This variant has also been reported in at least 5 probands with early-onset severe retinal dystrophy who were compound heterozygous with the NM_025114.4(CEP290):c.4024C>T (p.Gln1342Ter) variant or the NM_025114.4(CEP290):c.5850del (p.Phe1950fs) variant suspected in trans (1 point, PMID: 33970760, PMID: 17345604) or with the NM_025114.4(CEP290):c.297+1G>T variant, the NM_025114.4(CEP290):c.3904C>T (p.Gln1302Ter) variant, or the NM_025114.4(CEP290):c.1219_1220del (p.Met407GlufsTer14) variant confirmed in trans (3 points, PMID: 28973549, PMID: 32165824, PMID: 34196655), which were previously classified pathogenic by the ClinGen LCA/eoRD VCEP (4.5 total points, PM3_VeryStrong).

PM4_Supporting	✔	This variant is predicted to cause a change in the length of the protein due to an in-frame deletion encoding 1 amino acid in a non-repeat region, with at least one of the deleted base pairs highly conserved with a PhyloP conservation score of 7.37 (PM4_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of Leber congenital amaurosis (0.5 pts), onset before age 5 years (0.5 pts), extinguished electroretinogram responses from rods (0.5 pts) and cones (0.5 pts), central visual acuity limited to light perception (0.5 pts), white mottling in the peripheral pigmentation (0.5 pts), absence of vasculopathy / normal optic disc color, and decreased flash visual evoked potentials, with genotyping by next-generation sequencing identifying no alternative basis for retinal disease (2 pts), which together are specific for CEP290-related ciliopathy (total 5 points, PMID: 33970760, PP4).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a total allele frequency of 0.00002232, with 36 alleles / 1,612,700 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2_Supporting threshold of <0.0006 (PM2_Supporting).

Not Met criteria codes

BP2	✖	This variant has been reported in a proband with early-onset severe retinal dystrophy in cis with the NM_025114.4(CEP290):c.-1G>A variant and in trans with the NM_025114.4(CEP290):c.3904C>T (p.Gln1302Ter) variant (PMID: 32165824). However, the variant in cis has not yet been classified by the ClinGen LCA/eoRD VCEP, so BP2 is not met.

Curation History

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