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Variant: NM_000329.3(RPE65):c.304G>T (p.Glu102Ter)

Version: 1.0

CA226540

98863 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4fd71df2-0835-4077-8d17-9198d6ce82d4
Approved on: 2024/2/20
Published on: 2024/2/20

HGVS expressions

NM_000329.3(RPE65):c.304G>T (p.Glu102Ter)
NM_000329.3:c.304G>T
NC_000001.11:g.68444825C>A
CM000663.2:g.68444825C>A
NC_000001.10:g.68910508C>A
CM000663.1:g.68910508C>A
NC_000001.9:g.68683096C>A
NG_008472.1:g.10135G>T
NG_008472.2:g.10135G>T
ENST00000262340.6:c.304G>T
ENST00000262340.5:c.304G>T
NM_000329.2:c.304G>T

Pathogenic

Met criteria codes 5

PM3_Supporting PVS1 PM2_Supporting PP1 PP4

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 RPE65 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

NM_000329.3(RPE65):c.304G>T (p.Glu102Ter) is a nonsense variant that introduces a premature stop codon into exon 4 of 14, and is predicted to lead to nonsense-mediated decay in a gene in which loss-of-function is an established mechanism of disease (PVS1). This variant is present in gnomAD v.2.1.1 at a GrpMax allele frequency of 0.00004117, with 9 alleles / 113674 total alleles in the European (non-Finnish) population, which is lower than the ClinGen LCA / eoRD VCEP PM2_Supporting threshold of <0.0002 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including childhood onset, nystagmus (1 pt), nyctalopia, reduced visual acuity (1

pt), undetectable electroretinogram responses from rods (0.5 pts) and cones (1 pt), and decreased peripheral vision (1 pt), which together are specific for RPE65-related recessive retinopathy (4.5 total pts, PMID: 11095629, PP4). This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy who was homozygous for the variant (0.5 pts, PMID: 15512997, PM3_Supporting). The variant has been reported to segregate with childhood-onset severe retinal dystrophy through the proband plus 1 similarly affected relative, with the variant present in the homozygous state (PMID: 15512997, PP1). In summary, this variant meets the criteria to be classified as Pathogenic for RPE65-related recessive retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA / eoRD VCEP: PVS1, PM2_Supporting, PM3_Supporting, PP1, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PM3_Supporting	✔	The variant has been observed in a homozygous state in at least one proband (PMID: 15512997, PM3_Supporting). It has also been observed in the compound heterozygous state in an additional proband diagnosed with autosomal recessive retinitis pigmentosa (PMID: 11095629), however, this will not be considered for this curation to avoid circularity.
PVS1	✔	This nonsense variant introduces a prematures stop codon in exon 4 of 14 and is predicted to trigger nonsense-mediated decay (PVS1).
PM2_Supporting	✔	This variant has a PopMax Filtering AF of 0.00004117 (9/113674) in the European non-Finnish population in gnomAD v2.1.1 (with no homozygotes). This allele frequency is lower than the ClinGen LCA/eoRD VCEP threshold (<0.0002) for this criterion (PM2_Supporting).
PP1	✔	At least one proband with LCA has an affected sibling (PMID: 15512997, PP1).
PP4	✔	At least one proband displayed childhood onset (1 pt), nystagmus (1 pt), nyctalopia (required, 1 pt), reduced visual acuity (1 pt), undetectable rod electroretinogram (required, 1 pt), undetectable cone electroretinogram (1 pt) and decreased peripheral vision (1 pt), which together are specific for RPE65-related recessive retinopathy (PMID: 11095629, PP4).

Curation History

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