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Variant: NM_000329.3(RPE65):c.1360del (p.Thr454fs)

Version: 1.0

CA2573132571

1452575 (ClinVar)

Gene: RPE65 (HGNC:6121)
Condition: RPE65-related recessive retinopathy (MONDO:0100368)
Inheritance Mode: Autosomal recessive inheritance
UUID: bb754561-67bc-43f7-8fb6-5a8960491fe7
Approved on: 2024-04-22
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HGVS expressions

NM_000329.3:c.1360del
NM_000329.3(RPE65):c.1360del (p.Thr454fs)
NC_000001.11:g.68431158del
CM000663.2:g.68431158del
NC_000001.10:g.68896841del
CM000663.1:g.68896841del
NC_000001.9:g.68669429del
NG_008472.1:g.23805del
NG_008472.2:g.23805del
ENST00000262340.6:c.1360del
ENST00000262340.5:c.1360del
NM_000329.2:c.1360del

Pathogenic

Met criteria codes 4

PVS1 | PM2_Supporting | PP1 | PP4

Not Met criteria codes 1

PM3

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.1360del (p.Thr454LeufsTer?) is a frameshift variant that introduces a premature stop codon into exon 13 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 absent from gnomAD v.2.1.1 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including severely decreased ERG responses (0.5 pts), optic disc pallor (0.5 pts), pigmentary retinopathy with attenuated vessels (0.5 pts), symptomatic onset between birth and age five years (1 pt), decreased peripheral vision (1 pt), abnormal color vision (1 pt), decreased

central visual acuity (1 pt), and nystagmus (1 pt), which together are specific for RPE65-related recessive retinopathy (6.5 points, PMID: 28130426, PP4). 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 compound heterozygous state (PMID: 28130426, 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, PP1, and PP4. (VCEP specifications version 1.0.0; date of approval 09/21/2023).

Met criteria codes

PVS1	✔	The variant NM_000329.3(RPE65):c.1360del (p.Thr454LeufsTer?) in exon 13 causes a frameshift and premature stop codon and it's transcript is predicted to undergo nonsense mediated decay (PVS1).
PM2_Supporting	✔	NM_000329.3(RPE65):c.1360del (p.Thr454LeufsTer?) is absent from gnomAD v.2.1.1 (PM2_Supporting).
PP1	✔	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 compound heterozygous state (PP1; PMID: 28130426).
PP4	✔	At least one proband (RF.T.111, patient II-I) harboring this variant exhibits a phenotype including severely decrease ERG responses (0.5), optic disc pallor (0.5), pigmentary retinopathy with attenuated vessels (0.5), symptomatic onset between birth an age five years (1), decreased peripheral vision (1), abnormal color vision (1), decreased central visual acuity (1), and nystagmus (1), which together are specific for RPE65-related recessive retinopathy (6.5 points, PMID: 28130426, PP4).

Not Met criteria codes

PM3	✖	The variant NM_000329.3(RPE65):c.1360del (p.Thr454LeufsTer?) is in trans with NM_000329.3(RPE65):c.755T>C (p.Phe252Ser), which has not been evaluated by the LCA/eoRD VCEP yet (PM3_not met).

Curation History

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