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Variant: NM_000162.5(GCK):c.1361C>A (p.Ala454Glu)

Version: 1.0

CA16609264

393447 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 5373061c-5c70-4d02-bd9c-c75b82ee851e
Approved on: 2024/3/31
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HGVS expressions

NM_000162.5:c.1361C>A
NM_000162.5(GCK):c.1361C>A (p.Ala454Glu)
NC_000007.14:g.44145173G>T
CM000669.2:g.44145173G>T
NC_000007.13:g.44184772G>T
CM000669.1:g.44184772G>T
NC_000007.12:g.44151297G>T
NG_008847.1:g.49251C>A
NG_008847.2:g.57998C>A
ENST00000395796.8:c.*1359C>A
ENST00000616242.5:c.*481C>A
ENST00000683378.1:n.587C>A
ENST00000336642.9:c.395C>A
ENST00000345378.7:c.1364C>A
ENST00000403799.8:c.1361C>A
ENST00000671824.1:c.1424C>A
ENST00000672743.1:n.373C>A
ENST00000673284.1:c.1361C>A
ENST00000336642.8:c.413C>A
ENST00000345378.6:c.1364C>A
ENST00000395796.7:c.1358C>A
ENST00000403799.7:c.1361C>A
ENST00000437084.1:c.1310C>A
ENST00000459642.1:n.741C>A
ENST00000616242.4:c.1358C>A
NM_000162.3:c.1361C>A
NM_033507.1:c.1364C>A
NM_033508.1:c.1358C>A
NM_000162.4:c.1361C>A
NM_001354800.1:c.1361C>A
NM_001354801.1:c.350C>A
NM_001354802.1:c.221C>A
NM_001354803.1:c.395C>A
NM_033507.2:c.1364C>A
NM_033508.2:c.1358C>A
NM_033507.3:c.1364C>A
NM_033508.3:c.1358C>A

NM_001354803.2:c.395C>A

Likely Pathogenic

Met criteria codes 5

PS4_Moderate PP2 PP3 PS3_Moderate PM2_Supporting

Not Met criteria codes 1

PM1

Evidence Links 0

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1361C>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to glutamic acid at codon 454 (p.(Ala454Glu)) of NM_000162.5. GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.965, which is greater than the MDEP VCEP threshold of 0.70 (PP3). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.04, which is below the MDEP cutoff (<0.5) (PMID: 28842611). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 6 unrelated individuals with hyperglycemia (PS4_Moderate; ClinVar: 393447, PMIDs: 36257325, 20337973, 16602010, 17204055, internal lab contributors). In summary, c.1361C>A meets the criteria to be classified as likely pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PS3_Moderate, PS4_Moderate, PP2, PP3, PM2_Supporting.

Met criteria codes

PS4_Moderate	✔	This variant was identified in 6 unrelated individuals with hyperglycemia (PS4_Moderate; ClinVar: 393447, PMIDs: 36257325, 20337973, 16602010, 17204055, internal lab contributors).
PP2	✔	GCK is defined by the ClinGen MDEP as a gene that has a low rate of benign missense variation and has pathogenic missense variants as a common mechanism of disease (PP2).
PP3	✔	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.965, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.04, which is below the MDEP cutoff (<0.5) (PMID: 28842611).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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