The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_033508.3:c.686G>A

Version: 1.1

CA367400776

2628366 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 696d9e69-b348-4fef-b761-af0194764032
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HGVS expressions

NM_033508.3:c.686G>A
NC_000007.14:g.44147824C>T
CM000669.2:g.44147824C>T
NC_000007.13:g.44187423C>T
CM000669.1:g.44187423C>T
NC_000007.12:g.44153948C>T
NG_008847.1:g.46600G>A
NG_008847.2:g.55347G>A
ENST00000395796.8:c.*687G>A
ENST00000616242.5:c.689G>A
ENST00000345378.7:c.692G>A
ENST00000403799.8:c.689G>A
ENST00000671824.1:c.689G>A
ENST00000673284.1:c.689G>A
ENST00000345378.6:c.692G>A
ENST00000395796.7:c.686G>A
ENST00000403799.7:c.689G>A
ENST00000437084.1:c.638G>A
ENST00000616242.4:c.686G>A
NM_000162.3:c.689G>A
NM_033507.1:c.692G>A
NM_033508.1:c.686G>A
NM_000162.4:c.689G>A
NM_001354800.1:c.689G>A
NM_033507.2:c.692G>A
NM_033508.2:c.686G>A
NM_000162.5:c.689G>A
NM_033507.3:c.692G>A

Pathogenic

Met criteria codes 7

PP1_Strong PP2 PP3 PM1 PS4_Moderate PM2_Supporting PP4_Moderate

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.689G>A variant in the glucokinase gene, GCK, causes an amino acid change of cysteine to tyrosine at codon 230 (p.(Cys230Tyr)) 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 resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1), and is predicted to be deleterious by computational evidence, with a REVEL score of 0.966, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). This variant was identified in 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 3547291, 30663027, 25306193, internal lab contributors), including an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID: 35472491, internal lab contributors). This variant segregated with diabetes/hyperglycemia, with 8 informative meioses in a 3 families (PP1_Strong; PMID: 35472491, internal lab contributors). In summary, the c.689G>A variant meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.3.0, approved 8/11/2023): PP1_Strong, PP4_Moderate, PS4_Moderate, PM1, PP2, PP3, PM2_Supporting.

Met criteria codes

PP1_Strong	✔	This variant segregated with diabetes/hyperglycemia, with 8 informative meioses in a 3 families (PMID: 35472491, 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 0.966, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PM1	✔	This variant resides in an amino acid that directly binds glucose, which is defined as critical for the protein's function by the ClinGen MDEP (PM1).
PS4_Moderate	✔	This variant was identified in 5 unrelated individuals with hyperglycemia (PS4_Moderate; PMIDs: 3547291, 30663027, 25306193, internal lab contributors).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; PMID: 35472491, internal lab contributors).

Curation History

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