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Variant: NM_000162.5(GCK):c.544G>A (p.Val182Met)

Version: 1.0

CA152954

129144 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 2d2b85de-cab6-4f52-90ac-1e3bc29a8f81
Approved on: 2025/2/7
Published on: 2025/2/28

HGVS expressions

NM_000162.5(GCK):c.544G>A (p.Val182Met)
NM_000162.5:c.544G>A
NC_000007.14:g.44150004C>T
CM000669.2:g.44150004C>T
NC_000007.13:g.44189603C>T
CM000669.1:g.44189603C>T
NC_000007.12:g.44156128C>T
NG_008847.1:g.44420G>A
NG_008847.2:g.53167G>A
ENST00000395796.8:c.*542G>A
ENST00000616242.5:c.544G>A
ENST00000682635.1:n.1030G>A
ENST00000345378.7:c.547G>A
ENST00000403799.8:c.544G>A
ENST00000671824.1:c.544G>A
ENST00000673284.1:c.544G>A
ENST00000345378.6:c.547G>A
ENST00000395796.7:c.541G>A
ENST00000403799.7:c.544G>A
ENST00000437084.1:c.493G>A
ENST00000616242.4:c.541G>A
NM_000162.3:c.544G>A
NM_033507.1:c.547G>A
NM_033508.1:c.541G>A
NM_000162.4:c.544G>A
NM_001354800.1:c.544G>A
NM_033507.2:c.547G>A
NM_033508.2:c.541G>A
NM_033507.3:c.547G>A
NM_033508.3:c.541G>A

Pathogenic

Met criteria codes 7

PM2_Supporting | PP4_Moderate | PS3_Moderate | PS4 | PP1 | PP2 | PP3

Evidence Links 1

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.544G>A variant in the glucokinase gene, GCK, causes an amino acid change of valine to methionine at codon 182 (p.(Val182Met)) 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 absent from gnomAD v2.1.1 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.937, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Functional assays were performed where the MDEP wild type quality control measures were met, and showed that the relative activity Index (RAI) of this variant was 0.02, which is below the MDEP cutoff (<0.5) (PS3_Moderate, PMID: 10525657). Furthermore, this variant was identified in at least 12 unrelated individuals with hyperglycemia (PS4; PMID: 8433729, 10754480, 14517956, 25306193, 29510678, 31968686, 34496959, 35737141). At least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and macrosomia in normoglycemic offspring) (PP4_Moderate; PMID: 34406393). Additionally, this variant segregated with hyperglycemia with 2 informative meioses in 2 families (PP1; PMIDs: 25494859, 29510678). In summary, c.544G>A 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 08/11/2023): PP1, PP2, PP3, PP4_Moderate, PM2_Supporting, PS3_Moderate, PS4.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate	✔	This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and macrosomia in normoglycemic offspring) (PP4_Moderate; PMID: 34406393).
PS3_Moderate	✔	MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.02, which is below the MDEP cutoff (<0.5) (PS3_Moderate, PMID: 10525657). MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.02, which is below the MDEP cutoff (<0.5) PubMed:10525657
PS4	✔	This variant was identified in at least 12 unrelated individuals with hyperglycemia (PS4; PMID: 8433729, 10754480, 14517956, 25306193, 29510678, 31968686, 34496959, 35737141).
PP1	✔	This variant segregated with hyperglycemia with 2 informative meioses in 2 families (PP1; PMIDs: 25494859, 29510678).

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 0.937, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Curation History

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