

Variant: NM_000162.5(GCK):c.478G>A (p.Asp160Asn)

Version: 1.0

CA367401849 [↗](#)

447404 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: 13354932-69db-4514-a2f6-05aca270081f

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HGVS expressions

NM_000162.5(GCK):c.478G>A (p.Asp160Asn)

NM_000162.5:c.478G>A

NC_000007.14:g.44150961C>T

CM000669.2:g.44150961C>T

NC_000007.13:g.44190560C>T

CM000669.1:g.44190560C>T

NC_000007.12:g.44157085C>T

NG_008847.1:g.43463G>A

NG_008847.2:g.52210G>A

ENST00000395796.8:c.*476G>A

ENST00000616242.5:c.478G>A

ENST00000682635.1:n.964G>A

ENST00000345378.7:c.481G>A

ENST00000403799.8:c.478G>A

ENST00000671824.1:c.478G>A

ENST00000673284.1:c.478G>A

ENST00000345378.6:c.481G>A

ENST00000395796.7:c.475G>A

ENST00000403799.7:c.478G>A

ENST00000437084.1:c.427G>A

ENST00000616242.4:c.475G>A

NM_000162.3:c.478G>A

NM_033507.1:c.481G>A

NM_033508.1:c.475G>A

NM_000162.4:c.478G>A

NM_001354800.1:c.478G>A

NM_033507.2:c.481G>A

NM_033508.2:c.475G>A

NM_033507.3:c.481G>A

NM_033508.3:c.475G>A

Pathogenic

Met criteria codes 7

PP4_ModeratePS3_ModeratePP2PP3PP1_StrongPS4PM2_Supporting

Not Met criteria codes 2

PM1PM5

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 3.1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.478G>A variant in the glucokinase gene, GCK, causes an amino acid change of aspartate to asparagine at codon 160 (p.(Asp160Asn)) 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 has a Grpmax filtering allele frequency of 7.90e-7 in gnomAD v4.1.0, which is below the ClinGen MDEP threshold of 0.000003 (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.712, 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 0.29 (recalculated using updated RAI equation), which is below the MDEP cutoff (<0.5) (PMID: 25015100). This variant was identified in at least 33 unrelated individuals with hyperglycemia (PS4; PMID: 36257325, 25015100, internal lab contributors). Furthermore, at least one of these individuals had a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% detected incidentally in a pediatric patient and antibody negative) (PP4_Moderate; internal lab contributors). This variant segregated with hyperglycemia, with at least 21 informative meioses in ten families with hyperglycemia (PP1_Strong; PMID: 25015100, 36257325, internal lab contributors). Other missense variants at the same amino acid position have been classified as pathogenic (c.478G>C (p.Asp160His)) and likely pathogenic (c.480T>A and c.480T>G (p.Asp160Glu)); however, PM5 was not applied to avoid circularity as p.Asp160Asn contributed to the classification of the other variants at this residue. In summary, c.478G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 3.1.0, approved 10/10/2025): PS4, PP1_Strong, PS3_Moderate, PP4_Moderate, PP2, PP3, PM2_Supporting

Met criteria codes			
PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% detected incidentally in a pediatric patient and antibody negative) (PP4_Moderate; internal lab contributors).
PS3_Moderate			MDEP wild type quality control measures were met, and the relative activity Index (RAI) of this variant was found to be 0.29 (recalculated using updated RAI equation), which is below the MDEP cutoff (<0.5) (PMID: 25015100).
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 0.712, which is greater than the MDEP VCEP threshold of 0.70 (PP3).
PP1_Strong			

This variant segregated with hyperglycemia, with at least 21 informative meioses in ten families with hyperglycemia (PP1_Strong; PMID: 25015100, 36257325, internal lab contributors)

PS4			This variant was identified in at least 33 unrelated individuals with hyperglycemia (PS4; PMID: 36257325, 25015100, internal lab contributors).
PM2_Supporting			This variant has a Grpmax filtering allele frequency of 7.90e-7 in gnomAD v4.1.0, which is below the ClinGen MDEP threshold of 0.000003 (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
PM5			Other missense variants at the same amino acid position have been classified as pathogenic (c.478G>C (p.Asp160His)) and likely pathogenic (c.480T>A and c.480T>G (p.Asp160Glu)); however, PM5 was not applied to avoid circularity as p.Asp160Asn contributed to the classification of the other variants at this residue.

Curation History



 

 

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