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Variant: NM_033508.3:c.159T>G

Version: 1.0

CA4239711

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: d5a1c9a7-df83-4702-b2c2-a79305f75288
Approved on: 2024/12/2
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HGVS expressions

NM_033508.3:c.159T>G
NC_000007.14:g.44153347A>C
CM000669.2:g.44153347A>C
NC_000007.13:g.44192946A>C
CM000669.1:g.44192946A>C
NC_000007.12:g.44159471A>C
NG_008847.1:g.41077T>G
NG_008847.2:g.49824T>G
ENST00000395796.8:c.*160T>G
ENST00000616242.5:c.162T>G
ENST00000682635.1:n.648T>G
ENST00000345378.7:c.165T>G
ENST00000403799.8:c.162T>G
ENST00000671824.1:c.162T>G
ENST00000673284.1:c.162T>G
ENST00000345378.6:c.165T>G
ENST00000395796.7:c.159T>G
ENST00000403799.7:c.162T>G
ENST00000437084.1:c.162T>G
ENST00000616242.4:c.159T>G
NM_000162.3:c.162T>G
NM_033507.1:c.165T>G
NM_033508.1:c.159T>G
NM_000162.4:c.162T>G
NM_001354800.1:c.162T>G
NM_033507.2:c.165T>G
NM_033508.2:c.159T>G
NM_000162.5:c.162T>G
NM_033507.3:c.165T>G

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP1_Strong PM2_Supporting PP2 PP3

Not Met criteria codes 3

Expert Panel

Monogenic Diabetes VCEP

Criteria Specification Information

BS1 PS4 PM1

Evidence Links 0

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.162T>G variant in the glucokinase gene, GCK, causes an amino acid change of serine to arginine at codon 54 (p.(Ser54Arg)) 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 0.713, which is greater than the MDEP VCEP threshold of 0.70 (PP3). This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to zero copies present in the European non-Finnish subpopulation and any other non-Founder subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting. There are three copies present in the European Finnish population; however, given that this is a Founder sub-population, PM2_Supporting will still be applied (PM2_Supporting). This variant was identified in at least 4 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however PS4_Moderate will not be applied at this time given that all cases were identified in the Finnish population (internal lab contributors). At least one of these individuals had 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; internal lab contributors). Additionally, this variant segregated with diabetes, with at least 4 informative meioses in multiple families (PP1_Strong; internal lab contributors). In summary, c.162T>G 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): PP2, PP3, PM2_Supporting, PP4_Moderate, PP1_Strong.

Met criteria codes

PP4_Moderate	✔	This variant was identified in at least one individual with a clinical history highly specific for GCK-hyperglycemia (fasting glucose 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).
PP1_Strong	✔	This variant segregated with diabetes, with at least 4 informative meioses in 4 families (PP1_Strong; internal lab contributors).
PM2_Supporting	✔	This variant has an incomputable gnomAD v2.1.1 Grpmax filtering allele frequency due to zero copies present in the European non-Finnish subpopulation and any other non-Founder subpopulation, thereby meeting the ClinGen MDEP threshold criteria for PM2_Supporting. There are three copies present in the European Finnish population; however, given that this is a Founder sub-population, PM2_Supporting will still be applied (PM2_Supporting).
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 0.713, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

Not Met criteria codes

BS1		✖	The Grpmax filtering allele frequency of the which falls below ClinGen MDEP-established cutoffs for BS1; thus, this criterion will be not applied.
PS4		✖	This variant was identified in at least 4 unrelated individuals with non-autoimmune and non-absolute/near-absolute insulin-deficient diabetes; however, PS4_Moderate will not be applied at this time given that all cases were identified in the Finnish population (internal lab contributors).
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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