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Variant: NM_001354803.2:c.397dup

Version: 1.0

CA2573102980

2578360 (ClinVar)

Gene: GCK (HGNC:2645)
Condition: monogenic diabetes (MONDO:0015967)
Inheritance Mode: Semidominant inheritance
UUID: 579e8430-0352-48b7-ae69-a21548395c33
Approved on: 2023/9/1
Published on: 2023/9/1

HGVS expressions

NM_001354803.2:c.397dup
NC_000007.14:g.44145172dup
CM000669.2:g.44145172dup
NC_000007.13:g.44184771dup
CM000669.1:g.44184771dup
NC_000007.12:g.44151296dup
NG_008847.1:g.49253dup
NG_008847.2:g.58000dup
ENST00000395796.8:c.*1361dup
ENST00000616242.5:c.*483dup
ENST00000683378.1:n.589dup
ENST00000336642.9:c.397dup
ENST00000345378.7:c.1366dup
ENST00000403799.8:c.1363dup
ENST00000671824.1:c.1426dup
ENST00000672743.1:n.375dup
ENST00000673284.1:c.1363dup
ENST00000336642.8:c.415dup
ENST00000345378.6:c.1366dup
ENST00000395796.7:c.1360dup
ENST00000403799.7:c.1363dup
ENST00000437084.1:c.1312dup
ENST00000459642.1:n.743dup
ENST00000616242.4:c.1360dup
NM_000162.3:c.1363dup
NM_033507.1:c.1366dup
NM_033508.1:c.1360dup
NM_000162.4:c.1363dup
NM_001354800.1:c.1363dup
NM_001354801.1:c.352dup
NM_001354802.1:c.223dup
NM_001354803.1:c.397dup
NM_033507.2:c.1366dup
NM_033508.2:c.1360dup
NM_000162.5:c.1363dup
NM_033507.3:c.1366dup
NM_033508.3:c.1360dup

Likely Pathogenic

Met criteria codes 2

PM2_Supporting PVS1

Not Met criteria codes 1

PP4

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 1.2.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Monogenic Diabetes VCEP

The c.1363dup variant in the glucokinase gene, GCK, causes a frameshift in the protein at codon 455 of NM_000162.5, adding 4 novel amino acids before encountering a stop codon (p.(Val455GlyfsTer4)). While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1; PMID: 19790256). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors). In summary, c.1363dup 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): PVS1, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PVS1	✔	While this variant, located in exon 10 of 10, is predicted to cause a premature stop codon and to escape nonsense mediated decay, it is in a functionally important region of a gene where loss-of-function is an established disease mechanism (PVS1; PMID: 19790256).

Not Met criteria codes

PP4	✖	This variant was identified in an individual with a phenotype suggestive of GCK-hyperglycemia; however, PP4 is unable to be evaluated due to insufficient clinical information (internal lab contributors).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001354803.2:c.397dup	Likely Pathogenic	Monogenic Diabetes	2023-09-01	1.0	ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.2.0	GCK

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