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_177438.2(DICER1):c.1408G>T (p.Glu470Ter)

Version: 1.0

CA10586458

254287 (ClinVar)

Gene: DICER1 (HGNC:23405)
Condition: dicer1 syndrome (MONDO:0017288)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5c12ee63-fea6-450a-8b8b-d08cd2bf3f94
Approved on: 2022/5/18
Published on: 2022/7/8

HGVS expressions

NM_177438.2(DICER1):c.1408G>T (p.Glu470Ter)
NM_177438.2:c.1408G>T
NC_000014.9:g.95117723C>A
CM000676.2:g.95117723C>A
NC_000014.8:g.95584060C>A
CM000676.1:g.95584060C>A
NC_000014.7:g.94653813C>A
NG_016311.1:g.44700G>T
ENST00000529720.2:c.1408G>T
ENST00000531162.7:c.1408G>T
ENST00000674628.2:c.1408G>T
ENST00000675540.2:c.1408G>T
ENST00000696733.1:c.1408G>T
ENST00000696734.1:c.1408G>T
ENST00000696736.1:c.1408G>T
ENST00000696737.1:c.1408G>T
ENST00000696920.1:n.1671G>T
ENST00000696921.1:n.2514G>T
ENST00000696922.1:n.1817G>T
ENST00000696923.1:c.1408G>T
ENST00000696924.1:c.1408G>T
ENST00000696925.1:n.1817G>T
ENST00000696927.1:n.1011G>T
ENST00000696928.1:n.1605G>T
ENST00000343455.8:c.1408G>T
ENST00000393063.6:c.1408G>T
ENST00000526495.6:c.1408G>T
ENST00000532939.3:c.1408G>T
ENST00000556045.6:c.1408G>T
ENST00000674628.1:c.1408G>T
ENST00000675995.1:c.1408G>T
ENST00000343455.7:c.1408G>T
ENST00000393063.5:c.1408G>T
ENST00000526495.5:c.1408G>T
ENST00000527414.5:c.1408G>T
ENST00000532458.1:n.112G>T
ENST00000541352.5:c.1408G>T

NM_001195573.1:c.1408G>T
NM_001271282.2:c.1408G>T
NM_001291628.1:c.1408G>T
NM_030621.4:c.1408G>T
NM_001271282.3:c.1408G>T
NM_001291628.2:c.1408G>T
NM_177438.3:c.1408G>T
NM_001395677.1:c.1408G>T
NM_001395678.1:c.1408G>T
NM_001395679.1:c.1408G>T
NM_001395680.1:c.1408G>T
NM_001395682.1:c.1408G>T
NM_001395683.1:c.1408G>T
NM_001395684.1:c.1408G>T
NM_001395685.1:c.1408G>T
NM_001395686.1:c.1126G>T
NM_001395687.1:c.1003G>T
NM_001395688.1:c.1003G>T
NM_001395689.1:c.1003G>T
NM_001395690.1:c.1003G>T
NM_001395691.1:c.841G>T
NM_001395692.1:c.1408G>T
NM_001395693.1:c.1408G>T
NM_001395694.1:c.1408G>T
NM_001395695.1:c.1408G>T
NM_001395696.1:c.1003G>T
NM_001395697.1:c.-161G>T
NM_001395698.1:c.1003G>T
NR_172715.1:n.1826G>T
NR_172716.1:n.1753G>T
NR_172717.1:n.1920G>T
NR_172718.1:n.1920G>T
NR_172719.1:n.1753G>T
NR_172720.1:n.1753G>T

Pathogenic

Met criteria codes 4

PVS1 PP4 PM2_Supporting PS4_Supporting

Not Met criteria codes 11

PM1 PM6 BA1 BS1 BS4 BS3 BP2 PS1 PS2 PS3 PP1

Evidence Links 0

Expert Panel

DICER1 and miRNA-Processing Gene VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen DICER1 and miRNA-Processing Gene Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for DICER1 Version 1*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

DICER1 and miRNA-Processing Gene VCEP

The NM_177438.2:c.1408G>T (p.Glu470Ter) variant in DICER1 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 9/27 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). This variant received a total of 1 phenotype points across 1 family meeting DICER1 VCEP phenotype specificity scoring criteria of 1-1.5 points (PS4_Supporting; PMIDs 26925222, 28323992, 30178239, 30339877). At least one patient with this variant was found to have a somatic second hit in a recognized DICER1 hotspot codon on tumor sequencing, which is highly specific for DICER1 syndrome (PP4, PMID 28323992). This variant is absent from gnomAD v2.1.1 and v3.1.1 (non-cancer) (PM2_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for DICER1 syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen DICER1 VCEP: (PVS1, PS4_supporting, PP4, PM2_supporting. (Bayesian Points: 11; VCEP specifications version 1; 02/11/2022)

Met criteria codes

PVS1	✔	Predicted to undergo NMD: Stop codon 5’ of p.Pro1850
PP4	✔	Somatic c.5126A>G (p.Asp1709Gly) identified in individual with nodular hyperplasia (PMID: 28323992)
PM2_Supporting	✔	Absent gnomAD v2.1.1 (non-cancer). Over 20x coverage in >90% individuals.
PS4_Supporting	✔	Identified in a family with features of DICER1 syndrome (PMID: 26925222, 28323992, 30178239, 30339877, internal laboratory contributors).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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