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_177438.3(DICER1):c.5428G>C (p.Asp1810His)

Version: 1.0

CA390864678

933083 (ClinVar)

Gene: DICER1 (HGNC:23405)
Condition: DICER1-related tumor predisposition (MONDO:0100216)
Inheritance Mode: Autosomal dominant inheritance
UUID: aecf4bc2-f2d1-40e3-9e99-914d56a1972f
Approved on: 2025-02-25
Published on: 2025-06-05

HGVS expressions

NM_177438.3:c.5428G>C
NM_177438.3(DICER1):c.5428G>C (p.Asp1810His)
NC_000014.9:g.95091302C>G
CM000676.2:g.95091302C>G
NC_000014.8:g.95557639C>G
CM000676.1:g.95557639C>G
NC_000014.7:g.94627392C>G
NG_016311.1:g.71121G>C
ENST00000529720.2:c.5428G>C
ENST00000531162.7:c.5428G>C
ENST00000674628.2:c.5428G>C
ENST00000675540.2:c.*2078G>C
ENST00000696733.1:c.*50G>C
ENST00000696734.1:c.*83G>C
ENST00000696735.1:n.2415G>C
ENST00000696736.1:c.5428G>C
ENST00000696920.1:n.5691G>C
ENST00000696921.1:n.6534G>C
ENST00000696922.1:n.8359G>C
ENST00000696923.1:c.*83G>C
ENST00000696924.1:c.*50G>C
ENST00000696925.1:n.8359G>C
ENST00000343455.8:c.5428G>C
ENST00000393063.6:c.5428G>C
ENST00000526495.6:c.5428G>C
ENST00000556045.6:c.*145G>C
ENST00000675540.1:c.3173G>C
ENST00000675995.1:c.*3744G>C
ENST00000343455.7:c.5428G>C
ENST00000393063.5:c.5428G>C
ENST00000526495.5:c.5428G>C
ENST00000527414.5:c.5428G>C
ENST00000527416.2:n.21G>C
ENST00000527554.2:n.121G>C
ENST00000541352.5:c.5365-193G>C
ENST00000556045.5:c.2122G>C
NM_001195573.1:c.5365-193G>C

NM_001271282.2:c.5428G>C
NM_001291628.1:c.5428G>C
NM_030621.4:c.5428G>C
NM_177438.2:c.5428G>C
NM_001271282.3:c.5428G>C
NM_001291628.2:c.5428G>C
NM_001395677.1:c.5428G>C
NM_001395678.1:c.5428G>C
NM_001395679.1:c.5428G>C
NM_001395680.1:c.5428G>C
NM_001395682.1:c.5428G>C
NM_001395683.1:c.5428G>C
NM_001395684.1:c.5428G>C
NM_001395685.1:c.5428G>C
NM_001395686.1:c.5146G>C
NM_001395687.1:c.5023G>C
NM_001395688.1:c.5023G>C
NM_001395689.1:c.5023G>C
NM_001395690.1:c.5023G>C
NM_001395691.1:c.4861G>C
NM_001395697.1:c.3745G>C
NR_172715.1:n.5846G>C
NR_172716.1:n.6030G>C
NR_172717.1:n.5940G>C
NR_172718.1:n.5863G>C
NR_172719.1:n.5696G>C
NR_172720.1:n.5899G>C

Uncertain Significance

Met criteria codes 4

PS3_Supporting PM1 PP3 PM2_Supporting

Not Met criteria codes 1

PM5

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 1.3.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

DICER1 and miRNA-Processing Gene VCEP

The NM_177438.3:c.5428G>C variant in DICER1 is a missense variant predicted to cause substitution of aspartic acid by histidine at amino acid 1810 (p.Asp1810His). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro cleavage assay carried out using immunopurified DICER1 variant showed that this variant reduces the capacity of the protein to produce 5p and 3p microRNAs from a pre-miRNA, indicating that this variant impacts protein function (PS3_Supporting; Wu 2018, McGill University). This variant resides in the p.D1810 metal ion-binding residue located in the RNase IIIb domain of DICER1, that is defined as a mutational hotspot and critical functional domain by the ClinGen DICER1 VCEP (PM1; PMID: 31342592). In silico tools predict damaging impact of the variant on protein

function (REVEL: 0.928) (PP3). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for DICER1-related tumor predisposition based on the ACMG/AMP criteria applied, as specified by the ClinGen DICER1 VCEP: PS3_Supporting, PM1, PM2_Supporting, PP3. (Bayesian Points: 5; VCEP specifications version 1.3.0; 02/25/2025). Although available evidence supports germline pathogenicity of recurrent DICER1 somatic hotspot variants (PMID: 26925222), the clinical significance of this variant in the germline remains uncertain at this time since it has not yet been observed in the germline of an individual with a recognized DICER1 phenotype.

Met criteria codes

PS3_Supporting	✔	In vitro cleavage assay carried out using immunopurified DICER1 variant showed that this variant reduces the capacity of the protein to produce 5p and 3p microRNAs from a pre-miRNA, indicating that this variant impacts protein function(PS3_Supporting; Wu 2018, McGill University).
PM1	✔	This variant resides in the D1810 metal ion-binding residue located in the RNase IIIb domain of DICER1, that is defined as a mutational hotspot and critical functional domain by the ClinGen DICER1 VCEP (PM1; PMID: 31342592).
PP3	✔	In silico tools predict damaging impact of the variant on protein function (REVEL: 0.928) (PP3).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM5	✖	Five different missense variants, c.5429A>T (p.Asp1810Val), c.5429A>G (p.Asp1810Gly), c.5428G>T (p.Asp1810Tyr), c.5428G>A (p.Asp1810Asn), in the same codon have been reported (ClinVar Variation ID: 933086, 933085, 933084, 933082, 933083). However, per VCEP specifications PM5 cannot be used as PM1 is used for this variant.

Curation History

Showing 1 to 1 of 1 rows