

Variant: NM_177438.3(DICER1):c.5113G>A (p.Glu1705Lys)

CA390865421 [↗](#)

932987 (ClinVar) [↗](#)

Gene: DICER1 ([HGNC:23405](#))

Condition: DICER1-related tumor predisposition ([MONDO:0100216](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: f086a53b-4033-4d0b-8cc9-b5f0fd9cbc34

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HGVS expressions

NM_177438.3(DICER1):c.5113G>A (p.Glu1705Lys)

NM_177438.3:c.5113G>A

NC_000014.9:g.95094139C>T

CM000676.2:g.95094139C>T

NC_000014.8:g.95560476C>T

CM000676.1:g.95560476C>T

NC_000014.7:g.94630229C>T

NG_016311.1:g.68284G>A

ENST00000343455.8:c.5113G>A

ENST00000393063.6:c.5113G>A

ENST00000526495.6:c.5113G>A

ENST00000556045.6:c.5113G>A

ENST00000675540.1:c.2858G>A

ENST00000675995.1:c.*3429G>A

ENST00000343455.7:c.5113G>A

ENST00000393063.5:c.5113G>A

ENST00000526495.5:c.5113G>A

ENST00000527414.5:c.5113G>A

ENST00000541352.5:c.5113G>A

ENST00000556045.5:c.1807G>A

NM_001195573.1:c.5113G>A

NM_001271282.2:c.5113G>A

NM_001291628.1:c.5113G>A

NM_030621.4:c.5113G>A

NM_177438.2:c.5113G>A

NM_001271282.3:c.5113G>A

NM_001291628.2:c.5113G>A

NM_001395677.1:c.5113G>A

NM_001395678.1:c.5113G>A

NM_001395679.1:c.5113G>A

NM_001395680.1:c.5113G>A

NM_001395682.1:c.5113G>A

NM_001395683.1:c.5113G>A

NM_001395684.1:c.5113G>A

NM_001395685.1:c.5113G>A

NM_001395686.1:c.4831G>A

NM_001395687.1:c.4708G>A

NM_001395688.1:c.4708G>A
NM_001395689.1:c.4708G>A
NM_001395690.1:c.4708G>A
NM_001395691.1:c.4546G>A
NM_001395697.1:c.3430G>A
NR_172715.1:n.5531G>A
NR_172716.1:n.5715G>A
NR_172717.1:n.5625G>A
NR_172718.1:n.5548G>A
NR_172719.1:n.5381G>A
NR_172720.1:n.5458G>A

Pathogenic

Met criteria codes 6

- PP3
- PM2_Supporting
- PS3_Supporting
- PM1
- PS2
- PS4_Supporting

Not Met criteria codes 7

- PP4
- BS3
- BS1
- BS2
- BP4
- PM5
- BA1

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 1.2.0
- [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.5113G>A variant in DICER1 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 1705 (p.Glu1705Lys). This variant has been identified as a de novo occurrence with constitutional mosaicism in one individual with pleuropulmonary blastoma type I and cystic nephroma (PS2; PS4_supporting; 26925222). This variant is absent from gnomAD v2.1.1 and v3.1.2 (non-cancer) (PM2_Supporting). In vitro cleavage assays performed in different cell lines have demonstrated that this variant fails to produce 5p microRNAs from a pre-miRNA, indicating that this variant impacts protein function (PS3_Supporting; 22187960, 23132766, 28862265). In silico tools predict damaging impact of the variant on protein function (REVEL: 0.925) (PP3). This variant resides in the p.E1705 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 summary, this variant meets the criteria to be classified as Pathogenic for DICER1-related tumor predisposition based on the ACMG/AMP criteria applied, as specified by the ClinGen DICER1 VCEP: PS2, PM2_Supporting, PS4_supporting, PS3_Supporting, PP3, PM1. (Bayesian Points: 10; VCEP specifications version 1.2.0; 01/09/2024).

Met criteria codes

PP3			In silico tools predict damaging impact of the variant on protein function (REVEL: 0.925) (PP3).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 and v3.1.2 (non-cancer) (PM2_Supporting).
PS3_Supporting			In vitro cleavage assays performed in different cell lines have demonstrated that this variant fails to produce 5p microRNAs from a pre-miRNA, indicating that this variant impacts protein function (PS3_Supporting; 22187960,

23132766, 28862265).

PM1			This variant resides in the p.E1705 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).
PS2			This variant has been identified as a de novo occurrence with constitutional mosaicism in one individual with pleuropulmonary blastoma type I and cystic nephroma (PS2_moderate; 26925222).
PS4_Supporting			This variant has been identified as a de novo occurrence with constitutional mosaicism in one individual with pleuropulmonary blastoma type I and cystic nephroma (PS4_supporting; 26925222). The following PMIDs were reviewed and this variant was described as a somatic finding; these PMIDs did not contribute evidence for this classification: 33135284; 33848213; 33922805; 33567437; 32629665; 31900434; 30260442; 30446821; 30266945; 29395683; 29753010; 28766837; 28323992; 27697588; 26983701; 26841698; 26428316; 24617712; 36121434; 37215607; 35986592; 31487013; 31487013; 29881993; 28654427; 27664536; 28825729; 29037807; 26033501; 27459524; 26033159; 24481001; 24909177; 24136150.

Not Met criteria codes

PP4			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
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			Two different missense variants, c.5115A>C (p.Glu1705Asp), and c.5113G>C (p.Glu1705Gln), in the same codon have been reported (ClinVar Variation IDs: 932990, 932988). However, these variants have not yet met the criteria to be classified as pathogenic by the ClinGen DICER VCEP and this rule cannot be applied in combination with PM1 (PM5 not met).
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

See Report	Preferred Variant Title	Classification ⓘ	Condition	Published Date	Version ⓘ	Criteria Specification	Gene
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No matching records found

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