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

Version: 1.0

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:c.5113G>A
NM_177438.3(DICER1):c.5113G>A (p.Glu1705Lys)
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
ENST00000529720.2:c.5113G>A
ENST00000531162.7:c.5113G>A
ENST00000674628.2:c.5113G>A
ENST00000675540.2:c.*1763G>A
ENST00000696733.1:c.5113G>A
ENST00000696734.1:c.5113G>A
ENST00000696735.1:n.2100G>A
ENST00000696736.1:c.5113G>A
ENST00000696920.1:n.5376G>A
ENST00000696921.1:n.6219G>A
ENST00000696922.1:n.5522G>A
ENST00000696923.1:c.5113G>A
ENST00000696924.1:c.5113G>A
ENST00000696925.1:n.5522G>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

PS2 PP3 PM2_Supporting PM1 PS3_Supporting PS4_Supporting

Not Met criteria codes 7

BA1 PP4 PM5 BS2 BS1 BS3 BP4

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

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).
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).
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).
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).
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

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4	✖	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).
BS2	✖	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

BS3		✖	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

Curation History

Showing 1 to 1 of 1 rows