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Variant: NM_177438.3(DICER1):c.2516C>T (p.Ser839Phe)

Version: 1.1

CA129336

30566 (ClinVar)

Gene: DICER1 (HGNC:23405)
Condition: DICER1-related tumor predisposition (MONDO:0100216)
Inheritance Mode: Autosomal dominant inheritance
UUID: efaf6fc3-d5c9-4c9e-90d0-aa736abfd98d
Approved on: 2026/2/24
Published on: 2026/3/23

HGVS expressions

NM_177438.3:c.2516C>T
NM_177438.3(DICER1):c.2516C>T (p.Ser839Phe)
NC_000014.9:g.95108014G>A
CM000676.2:g.95108014G>A
NC_000014.8:g.95574351G>A
CM000676.1:g.95574351G>A
NC_000014.7:g.94644104G>A
NG_016311.1:g.54409C>T
ENST00000529720.2:c.2516C>T
ENST00000531162.7:c.2516C>T
ENST00000674628.2:c.2516C>T
ENST00000675540.2:c.2516C>T
ENST00000696733.1:c.2516C>T
ENST00000696734.1:c.2516C>T
ENST00000696736.1:c.2516C>T
ENST00000696737.1:c.2516C>T
ENST00000696738.1:n.404C>T
ENST00000696920.1:n.2779C>T
ENST00000696921.1:n.3622C>T
ENST00000696922.1:n.2925C>T
ENST00000696923.1:c.2516C>T
ENST00000696924.1:c.2516C>T
ENST00000696925.1:n.2925C>T
ENST00000343455.8:c.2516C>T
ENST00000393063.6:c.2516C>T
ENST00000526495.6:c.2516C>T
ENST00000532939.3:c.2516C>T
ENST00000556045.6:c.2516C>T
ENST00000675540.1:c.338C>T
ENST00000675995.1:c.*832C>T
ENST00000343455.7:c.2516C>T
ENST00000393063.5:c.2516C>T
ENST00000526495.5:c.2516C>T
ENST00000527414.5:c.2516C>T
ENST00000541352.5:c.2516C>T
NM_001195573.1:c.2516C>T
NM_001271282.2:c.2516C>T

NM_001291628.1:c.2516C>T
NM_030621.4:c.2516C>T
NM_177438.2:c.2516C>T
NM_001271282.3:c.2516C>T
NM_001291628.2:c.2516C>T
NM_001395677.1:c.2516C>T
NM_001395678.1:c.2516C>T
NM_001395679.1:c.2516C>T
NM_001395680.1:c.2516C>T
NM_001395682.1:c.2516C>T
NM_001395683.1:c.2516C>T
NM_001395684.1:c.2516C>T
NM_001395685.1:c.2516C>T
NM_001395686.1:c.2234C>T
NM_001395687.1:c.2111C>T
NM_001395688.1:c.2111C>T
NM_001395689.1:c.2111C>T
NM_001395690.1:c.2111C>T
NM_001395691.1:c.1949C>T
NM_001395692.1:c.2516C>T
NM_001395693.1:c.2516C>T
NM_001395694.1:c.2516C>T
NM_001395695.1:c.2516C>T
NM_001395696.1:c.2111C>T
NM_001395697.1:c.833C>T
NR_172715.1:n.2934C>T
NR_172716.1:n.2861C>T
NR_172717.1:n.3028C>T
NR_172718.1:n.3028C>T
NR_172719.1:n.2861C>T
NR_172720.1:n.2861C>T

Likely Pathogenic

Met criteria codes 6

PP4 PM2_Supporting PP1_Moderate PS3_Supporting PS4_Supporting PS2_Supporting

Not Met criteria codes 11

PS1 PP3 PM1 PM5 BA1 BS2 BS1 BS4 BS3 BP4 BP2

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 1.4.0*
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.2516C>T variant in DICER1 is a missense variant predicted to cause substitution of serine by phenylalanine at amino acid 839 (p.Ser839Phe). This variant received a total of 1 phenotype point across 2 unrelated probands meeting DICER1 VCEP phenotype

specificity scoring criteria of 1-1.5 points (PS4_Supporting; PMIDs: 3799599, 21205968; Internal Contributors). All reported phenotypes to date have been thyroid phenotypes (multi-nodular goiter and thyroid cancer, including pediatric). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with pediatric thyroid cancer (PS2_Supporting; Internal lab contributors). 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-related tumor predisposition (PP4, PMIDs: 27459524, 26033159). The variant has been reported to segregate with multi-nodular goiter in 20 affected family members from 1 family (PP1_Moderate; PMIDs: 21205968). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). In vitro cleavage assay carried out using immunopurified DICER1 variant Ser839Phe showed that this variant reduces the capacity of the protein to produce 5p/3p microRNAs from a pre-miRNA, indicating that this variant impacts protein function (PS3_Supporting; Wu, McGill 2018; Torrez, University of Michigan 2023, PMID: 37333613). The computational predictor REVEL gives a score of 0.519, which is neither above nor below the thresholds predicting a damaging or benign impact on DICER1 function; splice predictors MaxEntScan and SpliceAI indicate no impact on splicing (PP3 and BP4 not met). In summary, this variant meets the criteria to be classified as Likely Pathogenic for DICER1-related tumor predisposition based on the ACMG/AMP criteria applied, as specified by the ClinGen DICER1 VCEP: PS4_Supporting, PS2_Supporting, PP4, PP1_Moderate, PM2_Supporting, PS3_Supporting. (Bayesian Points: 7; VCEP specifications version 1.4.0; 02/24/2026)

Met criteria codes

PP4	✔	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-related tumor predisposition (PP4, PMIDs: 27459524, 26033159).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP1_Moderate	✔	The variant has been reported to segregate with multi-nodular goiter in 20 affected family members from 1 family (PP1_Moderate; PMIDs: 21205968).
PS3_Supporting	✔	In vitro cleavage assay carried out using immunopurified DICER1 variant Ser839Phe showed that this variant reduces the capacity of the protein to produce 5p/3p microRNAs from a pre-miRNA, indicating that this variant impacts protein function (PS3_Supporting; Wu, McGill 2018; Torrez, University of Michigan 2023, PMID: 37333613).
PS4_Supporting	✔	This variant received a total of 1 phenotype point across 2 unrelated probands meeting DICER1 VCEP phenotype specificity scoring criteria of 1-1.5 points (PS4_Supporting; PMIDs: 3799599, 21205968; Internal Contributors). Note: all had thyroid phenotypes
PS2_Supporting	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with pediatric thyroid cancer (PS2_Supporting; Internal lab contributors).

Not Met criteria codes

PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The computational predictor REVEL gives a score of 0.519, which is neither above nor below the thresholds predicting a damaging or benign impact on DICER1 function; splice predictors MaxEntScan and SpliceAI indicate no impact on splicing (PP3 and BP4 not met).

PM1		✖	This variant does not reside within a region of the RNAse IIIb domain that is defined as a mutational hotspot or critical functional domain by the ClinGen DICER1 VCEP (PM1 not met).
PM5		✖	Another missense variant c.2516C>G (p.Ser839Cys) with Grantham score equal to or less than the current variant has been reported in the same codon (ClinVar Variation ID: 935119). However, this variant has not yet met the criteria to be classified as pathogenic by the ClinGen DICER1 VCEP (PM5 not met).
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	This variant has been seen in 1 unrelated female without tumors through age 50 (BS2 not met; Ambry).
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
BP4		✖	The computational predictor REVEL gives a score of 0.519, which is neither above nor below the thresholds predicting a damaging or benign impact on DICER1 function; splice predictors MaxEntScan and SpliceAI indicate no impact on splicing (PP3 and BP4 not met).
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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