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Variant: NM_177438.2(DICER1):c.5465A>T (p.Asp1822Val)

Version: 2.1

CA10586400

254350 (ClinVar)

Gene: DICER1 (HGNC:23405)
Condition: DICER1-related tumor predisposition (MONDO:0100216)
Inheritance Mode: Autosomal dominant inheritance
UUID: 47c2c6a7-8144-418e-b4d0-69c01b152e08
Approved on: Tue, 01 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_177438.2(DICER1):c.5465A>T (p.Asp1822Val)
NM_177438.2:c.5465A>T
NC_000014.9:g.95091265T>A
CM000676.2:g.95091265T>A
NC_000014.8:g.95557602T>A
CM000676.1:g.95557602T>A
NC_000014.7:g.94627355T>A
NG_016311.1:g.71158A>T
ENST00000529720.2:c.5465A>T
ENST00000531162.7:c.5465A>T
ENST00000674628.2:c.5465A>T
ENST00000675540.2:c.*2115A>T
ENST00000696733.1:c.*87A>T
ENST00000696734.1:c.*120A>T
ENST00000696735.1:n.2452A>T
ENST00000696736.1:c.5465A>T
ENST00000696920.1:n.5728A>T
ENST00000696921.1:n.6571A>T
ENST00000696922.1:n.8396A>T
ENST00000696923.1:c.*120A>T
ENST00000696924.1:c.*87A>T
ENST00000696925.1:n.8396A>T
ENST00000343455.8:c.5465A>T
ENST00000393063.6:c.5465A>T
ENST00000526495.6:c.5465A>T
ENST00000556045.6:c.*182A>T
ENST00000675540.1:c.3210A>T
ENST00000675995.1:c.*3781A>T
ENST00000343455.7:c.5465A>T
ENST00000393063.5:c.5465A>T
ENST00000526495.5:c.5465A>T
ENST00000527414.5:c.5465A>T
ENST00000527416.2:n.58A>T
ENST00000527554.2:n.158A>T
ENST00000541352.5:c.5365-156A>T
ENST00000556045.5:c.2159A>T
NM_001195573.1:c.5365-156A>T

NM_001271282.2:c.5465A>T
NM_001291628.1:c.5465A>T
NM_030621.4:c.5465A>T
NM_001271282.3:c.5465A>T
NM_001291628.2:c.5465A>T
NM_177438.3:c.5465A>T
NM_001395677.1:c.5465A>T
NM_001395678.1:c.5465A>T
NM_001395679.1:c.5465A>T
NM_001395680.1:c.5465A>T
NM_001395682.1:c.5465A>T
NM_001395683.1:c.5465A>T
NM_001395684.1:c.5465A>T
NM_001395685.1:c.5465A>T
NM_001395686.1:c.5183A>T
NM_001395687.1:c.5060A>T
NM_001395688.1:c.5060A>T
NM_001395689.1:c.5060A>T
NM_001395690.1:c.5060A>T
NM_001395691.1:c.4898A>T
NM_001395697.1:c.3782A>T
NR_172715.1:n.5883A>T
NR_172716.1:n.6067A>T
NR_172717.1:n.5977A>T
NR_172718.1:n.5900A>T
NR_172719.1:n.5733A>T
NR_172720.1:n.5936A>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PS3_Supporting PS4_Moderate PM1_Supporting

Not Met criteria codes 8

BA1 PM6 PVS1 BS1 BS4 BS3 PS1 PS2

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*
- **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.5465A>T variant in DICER1 is a missense variant predicted to cause substitution of aspartic acid by valine at amino acid 1822 (p.Asp1822Val). This variant received a total of 3 phenotype points across 3 unrelated probands meeting DICER1 VCEP phenotype specificity scoring criteria of 2-3.5 points (PMIDs: 26925222, 21266384) (PS4_Moderate). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). An in vitro cleavage assay using immunopurified DICER1 variant Asp1822Val showed that this variant reduces the capacity of the protein to produce 5p/3p microRNAs from a pre-miRNA, indicating that it impacts protein function (Wu 2018, McGill University) (PS3_Supporting). This variant resides within the RNase IIIb domain of DICER1, which is defined as a mutational hotspot and

critical functional domain by the ClinGen DICER1 VCEP (PMID: 31342592) (PM1_Supporting). In silico tools predict a damaging impact of the variant on protein function (REVEL: 0.954) (PP3). 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_Moderate, PM1_Supporting, PM2_supporting, PS3_Supporting, PP3. (VCEP specifications version 1.4.0) Based on Tavtigian et al 2020 (PMID:32720330), the total points applied = 6, which equates to a classification of likely pathogenic.

Met criteria codes

PM2_Supporting	✔	Absent in gnomAD. Coverage is >20X.
PP3	✔	REVEL=0.954; Splice AI Donor Gain Δ0.56 and Donor Loss Δ0.26; MaxEntScan cryptic donor GT site 64 (63?)nt upstream of 3’ ss, cryptic site 7.07 (up from 0) and native site 5.64 (unchanged)
PS3_Supporting	✔	Wu et al. 2018. PhD Thesis. "DICER1 syndrome: assays, associations and models" - Evaluated via in vitro cleavage assay per table 2.1; table 3.1; table 3.2 and 6.3 cleavage products = “Delayed to no 5p and 3p”; AKA Mutation 33; No reported paired somatic mutations identified yet.
PS4_Moderate	✔	3 points; Reported in 2 individuals with PPB (Brenneman et al. 2015. PMID: 26925222; 2 points); Reported in a proband with PPB (4y) and their parent with thyroid cysts (30y) (Family 11, Slade et al. 2011. PMID: 21266384; 1 point).
PM1_Supporting	✔	Missense variant in Rnase IIIb domain (p.Y1682 – p.S1846)

Not Met criteria codes

BA1	✖	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
PVS1	✖	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
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

Curation History

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