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_030621.4(DICER1):c.5125G>A (p.Asp1709Asn)

Version: 1.0

CA390865395

690480 (ClinVar)

Gene: DICER1 (HGNC:23405)
Condition: dicer1 syndrome (MONDO:0017288)
Inheritance Mode: Autosomal dominant inheritance
UUID: d7bb7946-aea7-4885-9715-4a46a61fd29f
Approved on: 2022-05-17
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HGVS expressions

NM_030621.4:c.5125G>A
NM_030621.4(DICER1):c.5125G>A (p.Asp1709Asn)
NC_000014.9:g.95094127C>T
CM000676.2:g.95094127C>T
NC_000014.8:g.95560464C>T
CM000676.1:g.95560464C>T
NC_000014.7:g.94630217C>T
NG_016311.1:g.68296G>A
ENST00000529720.2:c.5125G>A
ENST00000531162.7:c.5125G>A
ENST00000674628.2:c.5125G>A
ENST00000675540.2:c.*1775G>A
ENST00000696733.1:c.5125G>A
ENST00000696734.1:c.5125G>A
ENST00000696735.1:n.2112G>A
ENST00000696736.1:c.5125G>A
ENST00000696920.1:n.5388G>A
ENST00000696921.1:n.6231G>A
ENST00000696922.1:n.5534G>A
ENST00000696923.1:c.5125G>A
ENST00000696924.1:c.5125G>A
ENST00000696925.1:n.5534G>A
ENST00000343455.8:c.5125G>A
ENST00000393063.6:c.5125G>A
ENST00000526495.6:c.5125G>A
ENST00000556045.6:c.5125G>A
ENST00000675540.1:c.2870G>A
ENST00000675995.1:c.*3441G>A
ENST00000343455.7:c.5125G>A
ENST00000393063.5:c.5125G>A
ENST00000526495.5:c.5125G>A
ENST00000527414.5:c.5125G>A
ENST00000541352.5:c.5125G>A
ENST00000556045.5:c.1819G>A
NM_001195573.1:c.5125G>A
NM_001271282.2:c.5125G>A
NM_001291628.1:c.5125G>A

NM_177438.2:c.5125G>A
NM_001271282.3:c.5125G>A
NM_001291628.2:c.5125G>A
NM_177438.3:c.5125G>A
NM_001395677.1:c.5125G>A
NM_001395678.1:c.5125G>A
NM_001395679.1:c.5125G>A
NM_001395680.1:c.5125G>A
NM_001395682.1:c.5125G>A
NM_001395683.1:c.5125G>A
NM_001395684.1:c.5125G>A
NM_001395685.1:c.5125G>A
NM_001395686.1:c.4843G>A
NM_001395687.1:c.4720G>A
NM_001395688.1:c.4720G>A
NM_001395689.1:c.4720G>A
NM_001395690.1:c.4720G>A
NM_001395691.1:c.4558G>A
NM_001395697.1:c.3442G>A
NR_172715.1:n.5543G>A
NR_172716.1:n.5727G>A
NR_172717.1:n.5637G>A
NR_172718.1:n.5560G>A
NR_172719.1:n.5393G>A
NR_172720.1:n.5470G>A

Pathogenic

Met criteria codes 6

PM2_Supporting PS2_Very Strong PS4_Moderate PP3 PM1 PS3_Supporting

Not Met criteria codes 10

BS1 BS4 BS3 BP4 BP2 PS1 BA1 PP1 PP4 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*
- **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.5125G>A variant in DICER1 is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 1709 (p.Asp1709Asn). This variant received a total of 2 phenotype points across 2 unrelated probands meeting DICER1 VCEP phenotype specificity scoring criteria of 2-3.5 points (PS4_Moderate, PMIDs: 26925222, 26475046). In both probands, this variant was identified as a de novo occurrence with constitutional mosaicism (PS2_Very Strong; PMIDs: 26925222, 26475046). This variant is absent from gnomAD v2.1.1 and v3.1.1 (non-cancer) (PM2_Supporting). In vitro cleavage assays in HEK293 cells showed that this variant fails to produce 5p microRNAs from a pre-miRNA, indicating that this variant impacts protein function (PS3_Supporting, PMIDs: 22187960, 26545620). The computational predictor REVEL gives a score of 0.868, which is above the threshold of 0.75, evidence that correlates with impact to DICER1 function (PP3). This variant resides in the p.D1709 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 syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen DICER1 VCEP: PS4_Moderate, PS2_Very Strong, PM2_Supporting, PS3_Supporting, PP3, PM1. (Bayesian Points: 15; VCEP specifications version 1; 02/11/2022)

Met criteria codes

PM2_Supporting	✔	Allele is absent from gnomAD with >20x coverage in the region.
PS2_Very Strong	✔	Confirmed de novo (constitutional mosaicism) in 2 probands with high-specificity phenotypes. (PMIDs: 26925222, 26475046)
PS4_Moderate	✔	2 pts: 2 unrelated probands each with PPB and other DICER1-related phenotypes (PMIDs: 26925222, 26475046)
PP3	✔	REVEL = 0.868 >0.75; no predicted splice impact
PM1	✔	Putative missense variants affecting metal ion-binding residues (p.E1705, p.D1709, p.D1713, p.G1809, p.D1810, p.E1813)
PS3_Supporting	✔	In vitro cleavage assays show impaired 5p cleavage (PMIDs: 22187960, 26545620)

Not Met criteria codes

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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	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
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4		✖	Code NA for germline variants in hotspot codons
PM5		✖	Multiple other variants in same codon but none are VCEP-curated yet and mostly somatic. ClinVar variation IDs: 933032, 933031, 933030, 932992, 690453, 477242, 932994, 932993

Curation History

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