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# *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**: 2022/5/17
**Published on**: 2022/7/8

## *HGVS expressions*

**NM_030621.4(DICER1):c.5125G>A (p.Asp1709Asn)**
**NM_030621.4:c.5125G>A**
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

PM1 PS2_Very Strong PS4_Moderate PS3_Supporting PP3 PM2_Supporting

**Not Met criteria codes** 10

PM5 BA1 BS1 BS4 BS3 BP4 BP2 PS1 PP1 PP4

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**

| | | |
|---|---|---|
| **PM1** | ✔ | Putative missense variants affecting metal ion-binding residues (p.E1705, p.D1709, p.D1713, p.G1809, p.D1810, p.E1813) |
| **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) |
| **PS3_Supporting** | ✔ | In vitro cleavage assays show impaired 5p cleavage (PMIDs: 22187960, 26545620) |
| **PP3** | ✔ | REVEL = 0.868 >0.75; no predicted splice impact |
| **PM2_Supporting** | ✔ | Allele is absent from gnomAD with >20x coverage in the region. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **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 |
| **BA1** | ✖ | 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 |
| **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 |
| **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 |

## Curation History

Showing 1 to 1 of 1 rows

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