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Variant: NM_007373.3(SHOC2):c.519G>A (p.Met173Ile)

CA199174

181528 (ClinVar)

Gene: SHOC2 (HGNC:8036)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6b6330b2-05be-48be-a7e9-3e8e77d8e63b
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_007373.3(SHOC2):c.519G>A (p.Met173Ile)
NM_007373.3:c.519G>A
NC_000010.11:g.110964877G>A
CM000672.2:g.110964877G>A
NC_000010.10:g.112724635G>A
CM000672.1:g.112724635G>A
NC_000010.9:g.112714625G>A
NG_028922.1:g.50335G>A
ENST00000265277.10:c.519G>A
ENST00000451838.2:c.-242-35538G>A
ENST00000480155.2:n.755G>A
ENST00000685059.1:c.519G>A
ENST00000685613.1:c.519G>A
ENST00000687592.1:n.818G>A
ENST00000688928.1:c.519G>A
ENST00000689118.1:c.519G>A
ENST00000689300.1:c.519G>A
ENST00000689997.1:c.-380-20751G>A
ENST00000691151.1:n.811G>A
ENST00000691369.1:c.519G>A
ENST00000691441.1:c.519G>A
ENST00000691903.1:c.519G>A
ENST00000692776.1:c.519G>A
ENST00000369452.9:c.519G>A
ENST00000265277.9:c.519G>A
ENST00000369452.8:c.519G>A
ENST00000451838.1:c.27G>A
ENST00000489390.1:n.56-35538G>A
NM_001269039.1:c.519G>A
NM_001269039.2:c.519G>A
NM_001324336.1:c.519G>A
NM_001324337.1:c.519G>A
NR_136749.1:n.116-20751G>A
NM_007373.4:c.519G>A
NM_001269039.3:c.519G>A
NM_001324336.2:c.519G>A
NM_001324337.2:c.519G>A

NR_136749.2:n.55-20751G>A

Pathogenic

Met criteria codes 4

PP3 PM2_Supporting PS2_Very Strong PS4

Not Met criteria codes 4

BA1 BS1 BP4 PS3

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SHOC2 Version 2.1.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The c.519G>A variant in the SHOC2 gene is a missense variant predicted to cause substitution of methionine by isoleucine at amino acid 173 (p.Met173Ile). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.768 (PP3). This variant has been identified as a de novo occurrence with confirmed parental relationships in 3 individuals and with unconfirmed parental relationships in 1 individual with RASopathy (PS2_VeryStrong; Invitae, GeneDx, Ambry, Genomic Medicine Lab; ClinVar SCV001573982.4, SCV000209055.14, SCV002641556.1, SCV001573024.1). This variant has been reported in more than 5 probands diagnosed with RASopathy (PS4; PMIDs: 25137548, 29907801; Invitae, GeneDx, UCSF Genomic Medicine Lab, LabCorp, Ambry; ClinVar SCV001573982.4, SCV000209055.14, SCV001573024.1, SCV000699327.2, SCV002641556.1). ERK phosphorylation assays showed that this variant decreases the ability of SHOC2 to accelerate ERK1/2 phosphorylation (PS3 not met, PMID: 25137548). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on the ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS2_VeryStrong, PS4, PM2_Supporting, PP3 (Specification Version 2.1, 09/17/2024)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.768 and is evolutionarily conserved (PP3)
PM2_Supporting	✔	This variant was absent from gnomAD v4.1.0
PS2_Very Strong	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in 3 individuals and as a de novo occurrence with unconfirmed parental relationships in 1 individual with RASopathy (PS2_VeryStrong; Invitae, GeneDx, Ambry, Genomic Medicine Lab; ClinVar SCV001573982.4, SCV000209055.14, SCV002641556.1, SCV001573024.1).
PS4	✔	This variant has been reported in more than 5 probands diagnosed with RASopathy (PS4; PMIDs: 25137548, 29907801; Invitae, GeneDx, UCSF Genomic Medicine Lab, LabCorp, Ambry; ClinVar SCV001573982.4, SCV000209055.14, SCV001573024.1, SCV000699327.2, SCV002641556.1).

Not Met criteria codes

BA1	✖	This variant was absent from gnomAD v4.1.0
BS1	✖	This variant was absent from gnomAD v4.1.0
BP4	✖	The computational predictor REVEL gives a score of 0.768 and is evolutionarily conserved (PP3)
PS3	✖	ERK phosphorylation assays showed that this variant decreases the ability of SHOC2 to accelerate ERK1/2 phosphorylation causing loss-of-function instead of gain-of-function (PS3 not met, PMID: 25137548).

Curation History

Showing 1 to 5 of 5 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_007373.3(SHOC2):c.519G>A (p.Me...	Pathogenic	RASopathy	2024-10-02	2.3	ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SHOC2 Version 2.1.0	SHOC2
View	NM_007373.3(SHOC2):c.519G>A (p.Me...	Pathogenic	RASopathy	2024-09-27	2.2	-	SHOC2
View	NM_007373.3(SHOC2):c.519G>A (p.Me...	Pathogenic	RASopathy	2024-09-27	2.1	-	SHOC2
View	NM_007373.3(SHOC2):c.519G>A (p.Me...	Pathogenic	RASopathy	2024-09-27	2.0	-	SHOC2
View	NM_007373.3(SHOC2):c.519G>A (p.Me...	Pathogenic	RASopathy	2024-09-27	1.0	-	SHOC2

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