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Variant: NM_005633.3(SOS1):c.512T>C (p.Val171Ala)

Version: 1.0

CA261743

45373 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 6d026472-974f-4b44-9918-65310c34a46d
Approved on: 2019/2/28
Published on: 2019/7/15

HGVS expressions

NM_005633.3(SOS1):c.512T>C (p.Val171Ala)
NM_005633.3:c.512T>C
NC_000002.12:g.39054822A>G
CM000664.2:g.39054822A>G
NC_000002.11:g.39281963A>G
CM000664.1:g.39281963A>G
NC_000002.10:g.39135467A>G
NG_007530.1:g.70642T>C
ENST00000461545.2:n.539T>C
ENST00000685782.1:n.1350T>C
ENST00000688189.1:n.277T>C
ENST00000689668.1:n.519T>C
ENST00000690679.1:c.612T>C
ENST00000690876.1:c.512T>C
ENST00000691229.1:c.512T>C
ENST00000692089.1:c.512T>C
ENST00000402219.8:c.512T>C
ENST00000395038.6:c.512T>C
ENST00000402219.6:c.512T>C
ENST00000426016.5:c.512T>C
NM_001382394.1:c.491T>C
NM_001382395.1:c.512T>C
NM_005633.4:c.512T>C

Likely Pathogenic

Met criteria codes 5

PS4_Supporting PP2 PM6 PM2 PM5

Not Met criteria codes 21

PVS1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PS3 PP1 PP3 PP4 BA1 PM1 PM3 PM4

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.512T>C (p.Val171Ala) variant in SOS1 has been reported as an unconfirmed de novo occurrence in a patient with clinical features of a Noonan spectrum disorder (PM6; Partners LMM internal data; GTR Lab ID: 21766; ClinVar SCV000062240.5). The p.Val171Ala variant has also been identified in another independent occurrences in patients with clinical features of a familial RASopathy (PS4_Supporting; PMID: 29402968). This variant was absent from large population studies (PM2; gnomAD, http://gnomAD.broadinstitute.org). A different pathogenic missense variant (p.Val171Gly) has been previously identified at this codon of SOS1 which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 40654). The variant is located in the SOS1 gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants and pathogenic missense variants are common (PP2; PMID: 29493581). In summary, this variant meets criteria to be classified as likely pathogenic for RASopathies in an autosomal dominant manner. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): PM6, PM5, PM2, PS4_Supporting, PP2.

Met criteria codes

PS4_Supporting	✔	Has also been identified in 1 patient w/possible familial RASopathy in Leung et al. 2018 PMID:29402968 Variant was identified in a patient with a possible familial RASopathy, see supplemental table. PubMed:29402968
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✔	The p.Val171Ala variant was identified in a de novo occurrence in one proband with clinical features of NS at the LMM.
PM2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✔	This variant is at the same codon as the p.Val171Gly variant which is classified as Pathogenic.

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	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
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	REVEL score = 0.566
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	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
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	In the supplement of Leung 2018 29402968 there is the following statment: "familal case(?Mother (with CoA) and siblings)" however this is not enough information to confirm segregation evidence.
PP3	✖	REVEL score = 0.566
PP4	✖	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
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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