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_005633.3:c.1867T>A

Version: 1.0

CA346365197

636262 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: e1a27f96-c415-42ee-a544-66d4c7ee7923
Approved on: 2019/2/28
Published on: 2019/7/15

HGVS expressions

NM_005633.3:c.1867T>A
NC_000002.12:g.39014838A>T
CM000664.2:g.39014838A>T
NC_000002.11:g.39241979A>T
CM000664.1:g.39241979A>T
NC_000002.10:g.39095483A>T
NG_007530.1:g.110626T>A
ENST00000685279.1:c.634T>A
ENST00000688043.1:n.2088T>A
ENST00000689668.1:n.1874T>A
ENST00000690876.1:c.1756T>A
ENST00000691229.1:c.1756T>A
ENST00000692089.1:c.1756T>A
ENST00000692620.1:c.634T>A
ENST00000402219.8:c.1867T>A
ENST00000395038.6:c.1867T>A
ENST00000402219.6:c.1867T>A
ENST00000426016.5:c.1867T>A
NM_001382394.1:c.1846T>A
NM_001382395.1:c.1867T>A
NM_005633.4:c.1867T>A

Likely Pathogenic

Met criteria codes 5

PM2 PS2 PS4_Supporting PP2 PP3

Not Met criteria codes 21

PVS1 BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2 PM6 PS1 PS3 PM1 PM3 PM5 BA1 PM4 PP1 PP4

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1867T>A (p.Phe623Ile) variant in SOS1 has been reported as a confirmed de novo occurrence in a patient with clinical features of Noonan syndrome (PS2; PMID 17586837, 20673819). The p.Phe623Ile variant has also been identified in another independent occurrence in a patient with clinical features of Noonan syndrome (PS4_Supporting; PMID 20673819). This variant was absent from large population studies (PM2; gnomAD; http://gnomad.broadinstitute.org). Computational prediction tools and conservation analysis suggest that the p.Phe623Ile variant may impact the protein (PP3). 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). Of note, two different pathogenic missense variants have been previously reported at this codon of SOS1 (p.Phe623Val and p.Phe623Glu) which may indicate that this residue is critical to the function of the protein, however these variants have not yet met the criteria to be classified as pathogenic (PM5 not met). 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): PS2, PS4_Supporting, PM2, PP2, PP3.

Met criteria codes

PM2	✔	Variant is absent from gnomAD
PS2	✔	(p.Phe623Ile) was identified in two probands with clinical features of Noonan syndrome, which occured de novo in 1 of these individuals with confirmed paternity (Zenker 2007, Fabretto 2010).
PS4_Supporting	✔	2 patients total have been described to have NS with the p.F623I variant, but one patient was counted towards PS2 for de novo. 1 separate case, therefore you can count as PS4_Supporting. This paper describes two unrelated patients with heterozygous p.F623I variants. Patient 1 is a novel occurance but pateint 2 is the same occurance from the de novo case reported in Zenker 2007. PubMed:20673819 This paper reports one of the sporadic NS cases that is de novo which has been confirmed. Applied PS2 for this case. Do not count towards PS4 because the patient described in this paper is the same pateint as "Patient 2" in Fabretto 2010. PubMed:17586837
PP2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✔	REVEL score of 0.733 >0.7 cutoff. Some crystal structure data suggests that the residue may interact with other residues but it is not confirmed functionally.

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	✖	Variant is absent from gnomAD
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	The p.Phe623Ile variant has not been functionally assessed specifically despite the p.Phe623Glu variant having been assessed and found to impact SOS1 activity. PS3 cannot be applied. "The F623E Sos mutant showed no apparent defect in Ras binding (Fig. 5B), but it did display a decrease in exchange activity (Fig. 5D). These results indicate that the N-terminal domain plays a role in maintaining Sos in a catalytically active conformation." PubMed:11333268 "Substitution of F623 by glutamate in a SOS1 mutant protein composed of the Rem-Cdc25 module has been shown to decrease exchange activity. Substitution of F623 by isoleucine presumably also abolishes aromatic interaction between F958 and F623 and may therefore lead to a reduced guanine nucleotide exchange activity of SOS1" PubMed:17586837
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 of 0.733 >0.7 cutoff. Some crystal structure data suggests that the residue may interact with other residues but it is not confirmed functionally.
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
PM6	✖	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
PS3	✖	The p.Phe623Ile variant has not been functionally assessed specifically despite the p.Phe623Glu variant having been assessed and found to impact SOS1 activity. PS3 cannot be applied. "The F623E Sos mutant showed no apparent defect in Ras binding (Fig. 5B), but it did display a decrease in exchange activity (Fig. 5D). These results indicate that the N-terminal domain plays a role in maintaining Sos in a catalytically active conformation." PubMed:11333268

"Substitution of F623 by glutamate in a SOS1 mutant protein composed of the Rem-Cdc25 module has been shown to decrease exchange activity. Substitution of F623 by isoleucine presumably also abolishes aromatic interaction between F958 and F623 and may therefore lead to a reduced guanine nucleotide exchange activity of SOS1"
PubMed:17586837

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
PM5	✖	If the p.Phe623Ile variant was pathogenic it could be used for p.Phe623Val to meet PM5 as that variant is on the borderline of VUS/LP, however, the p.Phe623Val variant cannot be used as evidence to support the usage of PM5 for this variant. Additionally, the p.Phe623Glu variant will be curated separately as it has been functionally assessed by Hall 2001 11333268.
BA1	✖	Variant is absent from gnomAD
PM4	✖	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	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.