

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

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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

PS4_Supporting PS2 PP2 PP3
PM2

Not Met criteria codes 21

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

Evidence Links 3

Expert Panel

RASopathy VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

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

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 occurrence but patient 2 is the same occurrence 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 patient as "Patient 2" in Fabretto 2010. PubMed:17586837 			
PS2			(p.Phe623Ile) was identified in two probands with clinical features of Noonan syndrome, which occurred de novo in 1 of these individuals with confirmed paternity (Zenker 2007, Fabretto 2010).
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.
PM2			Variant is absent from gnomAD

Not Met criteria codes

BA1			Variant is absent from gnomAD
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 
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
PVS1			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
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 [↗](#)

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
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.
PM4			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

Curation History [↗](#)



 

 

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