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(SOS1):c.1642A>C (p.Ser548Arg)

CA234977

40678 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 940ad8e1-71b4-424b-b085-ae78bed7e9d7
Approved on: 2017-04-03
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HGVS expressions

NM_005633.3:c.1642A>C
NM_005633.3(SOS1):c.1642A>C (p.Ser548Arg)
ENST00000395038.6:c.1642A>C
ENST00000402219.6:c.1642A>C
ENST00000426016.5:c.1642A>C
NC_000002.12:g.39022786T>G
CM000664.2:g.39022786T>G
NC_000002.11:g.39249927T>G
CM000664.1:g.39249927T>G
NC_000002.10:g.39103431T>G
NG_007530.1:g.102678A>C

Pathogenic

Met criteria codes 6

PP3 PP2 PM1 PM2 PS2_Very Strong PS3

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1642A>C (p.Ser548Arg) variant in SOS1 has been reported as a confirmed de novo occurrence in a patient with clinical features of a RASopathy (PS2_VeryStrong; PMID 17143282). In vitro functional studies provide some evidence that the p.Ser548Arg variant may impact protein function (PS3; PMID 23487764). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). 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). Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of SOS1 (PM1; PMID 29493581). Computational prediction tools and conservation analysis suggest that the p.Ser548Arg variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. Rasopathy-specific ACMG/AMP criteria applied (PMID: 29493581): PP2, PP3, PM1, PM2, PS3 PS2_VeryStrong.

Met criteria codes

PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Ser548Arg variant may impact the protein (PP3).
PP2	✔	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).
PM1	✔	Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of SOS1 (PM1; PMID 29493581). Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of SOS1 (PM1; PMID 29493581). PubMed:29493581
PM2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2_Very Strong	✔	The p.Arg552Gly variant in SOS1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17143282). The p.Arg552Gly variant in SOS1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17143282). PubMed:17143282
PS3	✔	In vitro functional studies provide some evidence that the p.Arg552Gly variant may impact protein function (PS3; PMID 17143285). In vitro functional studies provide some evidence that the p.Arg552Gly variant may impact protein function (PS3; PMID 17143285). PubMed:17143285

Curation History

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