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.1656G>T (p.Arg552Ser)

Version: 1.0

CA261730

40684 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: b1bb4dae-8f06-4a91-b1c4-ccf1a3d0092f
Approved on: 2019-05-10
Published on: 2019-06-28

HGVS expressions

NM_005633.3:c.1656G>T
NM_005633.3(SOS1):c.1656G>T (p.Arg552Ser)
ENST00000395038.6:c.1656G>T
ENST00000402219.6:c.1656G>T
ENST00000426016.5:c.1656G>T
NC_000002.12:g.39022772C>A
CM000664.2:g.39022772C>A
NC_000002.11:g.39249913C>A
CM000664.1:g.39249913C>A
NC_000002.10:g.39103417C>A
NG_007530.1:g.102692G>T

Pathogenic

Met criteria codes 7

PS1 PS2 PS4_Moderate PP2 PP3 PM1_Strong PM2

Not Met criteria codes 16

PS3 PP1 PM6 PM5 PM4 BA1 BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1656G>T (p.Arg552Ser) variant in SOS1 has been reported as a confirmed de novo occurrence in one patient and 2 other probands with clinical features of a RASopathy (PS2, PS4_Moderate; PMID 17586837, 18854871). Of note, one of these cases was an affected mother-child duo (PP1 not met; PMID: 17586837). This variant was absent from large population studies (PM2; gnomAD, http://gnomad.broadinstitute.org). This amino acid residue has been designated as a hotspot. These variants would have received PM5_Strong but the RAS EP decided that PM1 and PM5 cannot be used simultaneously and therefore this rule has been upgraded with expert judgement (PM1_Strong). Of note, the p.Arg552Ser variant in SOS1 has also been a consequence of the c.1656G>C nucleotide change which has been classified as pathogenic (PS1; ClinVar ID 12872). Computational prediction tools and conservation analysis suggest

that the p.Arg552Ser 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). 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): PS2, PS1, PM1_Strong, PM2, PS4_Moderate, PP2, PP3.

Met criteria codes

PS1	✔	The c.1656G>C variant is classified as Pathogenic by the RAS EP.
PS2	✔	Variant identified in a confirmed de novo case. The c.1656G>T varinat was identified in 1 sporadic case and 1 familial observation. The familial observation was an affected mother-child duo. The sporadic case was confirmed to be de novo. The c.1656G>T varinat was identified in 1 sporadic case and 1 familial observation. The familial observation was an affected mother-child duo. The sporadic case was confirmed to be de novo. PubMed:17586837
PS4_Moderate	✔	This variant has been reported in at least 3 occurrences in the literature in patients with a RASopathy (PMID: 17586837, 18854871) Sequenced 75 index cases with syndromic MGCL and identified the p.Arg552Ser variant in a 28 year old female who was diagnosed with NS with MGCL at age 11. The patien has short stature, PS, ASD, Pectus deformation, webbed neck, curly hair, hearing impairment, ptosis. The inheritance of the variant is not described. PubMed:18854871 The c.1656G>T variant was identified in 1 sporadic case and 1 familial observation. The familial observation was an affected mother-child duo. The sporadic case was confirmed to be de novo. PubMed:17586837 In this paper, cancer samples were sequenced and they identified the p.Arg552Ser variant. They identified both the c.1656G>C and c.1656G>T variant, each in 1 occurrence. PubMed:29625050
PP2	✔	SOS1 gene is PP2 gene
PP3	✔	REVEL score 0.863
PM1_Strong	✔	This amino acid residue has been designated as a hotspot. These variants would have received PM5_Strong but the RAS EP decided that PM1 and PM5 cannot be used simultaneously and therefore this rule has been upgraded with expert judgement.
PM2	✔	this variant is absent from gnomAD.

Not Met criteria codes

PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	This variant was in a mother child pair with NS.

The c.1656G>T varinat was identified in 1 sporadic case and 1 familial observation. The familial observation was an affected mother-child duo. The sporadic case was confirmed to be de novo. PubMed:17586837

PM6	✖	The de novo case was said to be "confirmed" but may downgrade to PM6 if this isn't sufficient for PS2. The c.1656G>T varinat was identified in 1 sporadic case and 1 familial observation. The familial observation was an affected mother-child duo. The sporadic case was confirmed to be de novo. PubMed:17586837
PM5	✖	There are multiple missense variants at this codon that are pathogenic. These variants would have received PM5_Strong but the RAS EP decided that PM1 and PM5 cannot be used simultaneously and therefore this rule has been removed
PM4	✖	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
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	✖	The c.1656G>T varinat was identified in 1 sporadic case and 1 familial observation. The familial observation was an affected mother-child duo. The sporadic case was confirmed to be de novo. PubMed:17586837
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
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

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.