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.1654A>T (p.Arg552Trp)

Version: 1.0

CA16042455

372656 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: b80c62b7-b2c8-4d2d-97fd-f9770a74e570
Approved on: 2019-05-10
Published on: 2019-06-28

HGVS expressions

NM_005633.3:c.1654A>T
NM_005633.3(SOS1):c.1654A>T (p.Arg552Trp)
ENST00000395038.6:c.1654A>T
ENST00000402219.6:c.1654A>T
ENST00000426016.5:c.1654A>T
NC_000002.12:g.39022774T>A
CM000664.2:g.39022774T>A
NC_000002.11:g.39249915T>A
CM000664.1:g.39249915T>A
NC_000002.10:g.39103419T>A
NG_007530.1:g.102690A>T

Likely Pathogenic

The Expert Panel has overridden the computationally generated classification - "*Uncertain Significance - Insufficient Evidence*"

Met criteria codes 5

PM2 PS4_Supporting PP2 PP3 PM1_Strong

Not Met criteria codes 18

BS2 BS1 BS4 BS3 BP5 BP7 BP4 BP3 BP1 BP2 PM6 PS1 PS2 PS3 PM5 BA1 PM4 PP1

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1654A>T (p.Arg552Trp) variant has been identified in 1 patient with clinical features of a RASopathy (PS4_Supporting; PMID: 22465605). This variant was absent from large population studies (PM2; gnomAD, http://gnomad.broadinstitute.org). Of note this p.Arg552 residue is defined as a hotspot by the RAS VCEP. This variant would have received PM5_Strong but the RAS EP decided that PM1 and PM5 cannot be used simultaneously and therefore the PM1 rule has been upgraded with expert judgement (PM1_Strong). Computational prediction tools and conservation analysis suggest that the p.Arg552Trp 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): PS4_Supporting, PM2, PM1_Strong, PP2, PP3.

Met criteria codes

PM2	✔	Variant is absent from gnomAD
PS4_Supporting	✔	Collazo et al. 2012: Patient with NS with pulmonary stenosis, facial dysmorphism, and cryptochordism with a father with the variant and bilateral cryptochordism, normal stature and NS. Same patient as Ezquieta et al. 2012? Count as one case. Patient with NS with pulmonary stenosis, facial dysmorphism, and cryptochordism with a father with the variant and bilateral cryptochordism, normal stature and NS PubMed:22465605
PP2	✔	SOS1 is a PP2 gene
PP3	✔	Variant has REVEL score of 0.816
PM1_Strong	✔	p.Arg552 residue is defined 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.

Not Met criteria codes

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	✖	Same patient as described in Collazo et al. 2012 Variant segregated from father with NS to index patient PubMed:22465605
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	✖	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
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
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
PM5	✖	There are multiple Pathogenic variants at this codon. 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.
BA1	✖	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
PP1	✖	Collazo et al. 2012 Variant segregated from father with NS to index patient Same patient as described in Collazo et al. 2012 Variant segregated from father with NS to index patient PubMed:22465605

Curation History

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