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.1655G>T (p.Arg552Met)

Version: 1.0

CA16616762

40681 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: b58990d7-5f0e-4d39-bc5c-0202598cfebe
Approved on: 2019-05-10
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HGVS expressions

NM_005633.3(SOS1):c.1655G>T (p.Arg552Met)
NM_005633.3:c.1655G>T
ENST00000395038.6:c.1655G>T
ENST00000402219.6:c.1655G>T
ENST00000426016.5:c.1655G>T
NC_000002.12:g.39022773C>A
CM000664.2:g.39022773C>A
NC_000002.11:g.39249914C>A
CM000664.1:g.39249914C>A
NC_000002.10:g.39103418C>A
NG_007530.1:g.102691G>T

Likely Pathogenic

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

Met criteria codes 4

PS4_Moderate PM1_Strong PP2 PP3

Not Met criteria codes 19

PM5 PM4 PM6 PM2 BA1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PS1 PS2 PS3 PP1

Evidence Links 2

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1655G>T (p.Arg552Met) variant has been identified in at least 3 independent occurrences in patients with clinical features of a RASopathy (PS4_Moderate; GeneDx internal data; GTR Lab IDs 26957; SCV000565586.5 PMID: 21387466). his AA residue has been specified as a hotspot for variation. 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). Computational prediction tools and conservation analysis suggest that the p.Arg552Met 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 likely pathogenic for RASopathies in an autosomal dominant manner. RASopathy-specific ACMG/AMP criteria applied (PMID:29493581): PS4_Moderate, PM1_Strong, PP2, PP3.

Met criteria codes

PS4_Moderate	✔	GeneDx- Variant seen in a proband, sibling, and parent all with Noonan syndrome Invitae- observed p.Arg552Met once in patient with clinical features of RASopathy Didn't do additional family testing Lepri 2011: Patient NS25 is one patient with the p.Arg552Met variant Patient NS25: 11y 7m old Male with neonatal/infantile growth failure, short stature, delayed bone age, craniofacial anomalies, high forehead bitemporal narrowing, downslanting palpebral fissures and epicanthal folds has p.Arg552Met variant in sporadic case with inheritance unknown. This paper states that there are 2 patients with this variant and clinical features of NS but clinical information for the second patient is not available. PubMed:21387466 Sequenced over 9,000 tumors and identified the p.Arg552Met variant in one sample. PubMed:29625050
PM1_Strong	✔	This AA residue has been specified as a hotspot for variation. 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.
PP2	✔	Variant is in BRAF
PP3	✔	REVEL score = 0.903

Not Met criteria codes

PM5	✖	There are multiple Pathogenic variants at this codon: when all variants are assessed there should be at least 2 but specify which ones here. 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 and PM1 has been upgraded
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
PM2	✖	Variant has been identified in 1/111178 European (Non-Finnish) alleles in gnomAD.
BA1	✖	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	✖	

			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	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
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
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
PP1		✖	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

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