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Variant: NM_005633.3(SOS1):c.1655G>C (p.Arg552Thr)

Version: 1.0

CA261728

40682 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 29f14367-9d8d-4cd9-a97b-74d1d13b0a74
Approved on: 2019/4/23
Published on: 2024/8/23

HGVS expressions

NM_005633.3(SOS1):c.1655G>C (p.Arg552Thr)
NM_005633.3:c.1655G>C
NC_000002.12:g.39022773C>G
CM000664.2:g.39022773C>G
NC_000002.11:g.39249914C>G
CM000664.1:g.39249914C>G
NC_000002.10:g.39103418C>G
NG_007530.1:g.102691G>C
ENST00000472480.2:n.1535G>C
ENST00000685279.1:c.422G>C
ENST00000688043.1:n.1876G>C
ENST00000689668.1:n.1662G>C
ENST00000690876.1:c.1544G>C
ENST00000691229.1:c.1544G>C
ENST00000692089.1:c.1544G>C
ENST00000692620.1:c.422G>C
ENST00000402219.8:c.1655G>C
ENST00000395038.6:c.1655G>C
ENST00000402219.6:c.1655G>C
ENST00000426016.5:c.1655G>C
NM_001382394.1:c.1634G>C
NM_001382395.1:c.1655G>C
NM_005633.4:c.1655G>C

Pathogenic

Met criteria codes 6

PP2 PP3 PM1_Strong PM6 PM2 PS4_Moderate

Not Met criteria codes 20

PP1 PP4 BA1 PM3 PM5 PM4 PVS1 BS1 BS4 BS3 BS2 PS1 PS2 PS3 BP5 BP7 BP4 BP3 BP1 BP2

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>C (p.Arg552Thr) variant in SOS1 has been identified in at least 4 independent occurrences in patients with clinical features of a RASopathy, one of which was de novo (PS4_Moderate; GeneDx, St. George's Hospital, London internal data; GTR Lab ID: 26957 SCV000209121.12; PMID: 21387466, 19352411). This variant was absent from large population studies (PM2; gnomAD, http://gnomad.broadinstitute.org). The p.Arg552 residue has been defined as a hotspot by the RAS EP. 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). 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). Computational prediction tools and conservation analysis suggest that the p.Arg552Thr 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): PS4_Moderate, PM1_Strong, PM2, PM6, PP2, PP3.

Met criteria codes

PP2	✔	SOS1 is a PP2 gene
PP3	✔	Variant has REVEL score of 0.955
PM1_Strong	✔	This variant is at the hotspot that has been defined as p.Arg552. 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.
PM6	✔	GeneDx: Identified this variant in a de novo case of NS. Internal data.
PM2	✔	This variant is absent from gnomAD.
PS4_Moderate	✔	The c.1655G>C (p.Arg552Thr) variant in SOS1 has been identified in at least 4 independent occurrences in patients with clinical features of a RASopathy, one of which was de novo (PS4_Moderate; GeneDx, St. George's Hospital, London internal data; GTR Lab ID: 26957 SCV000209121.12; PMID: 21387466, 19352411). Four cohorts were included in this study...143 clinically well-characterized patients with NS of European/Italian ancestry, patients from the Sarkozy 2009 study, (N= 358) anonymous samples from individuals with phenotypes suggestive of NS from commercial DNA diagnostic testing, finally a cohort of 59 subjects with nonsyndromic CHD's. The variant was identified in 1 patient with an unknown family history. This was a large study of patients with clinical features of a RASopathy that has been described elsewhere. PubMed:21387466 Patient 2 of the 5 patients reported in this study was sequenced and determined to have the p.Arg552Thr variant. the patient had typical NS, cryporchidism, decreased platelet aggregation, moderate ventriculomegaly, intellectual disability PubMed:19352411

Not Met criteria codes

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
BA1		✖	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		✖	There are multiple pathogenic variants that have been reported 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 with expert judgement.
PM4		✖	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
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
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
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

Curation History

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