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Variant: NM_005633.3(SOS1):c.1655G>A (p.Arg552Lys)

Version: 1.0

CA261726

40683 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1065305a-be0c-4399-99c0-352adbd087b7
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HGVS expressions

NM_005633.3(SOS1):c.1655G>A (p.Arg552Lys)
NM_005633.3:c.1655G>A
NC_000002.12:g.39022773C>T
CM000664.2:g.39022773C>T
NC_000002.11:g.39249914C>T
CM000664.1:g.39249914C>T
NC_000002.10:g.39103418C>T
NG_007530.1:g.102691G>A
ENST00000395038.6:c.1655G>A
ENST00000402219.6:c.1655G>A
ENST00000426016.5:c.1655G>A

Pathogenic

Met criteria codes 7

PP2 PP3 PM1_Strong PM2 PS3 PS4 PS2_Very Strong

Not Met criteria codes 16

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

Evidence Links 11

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1655G>A (p.Arg552Lys) 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 17586837, 17143282, 30266093, 26686981). This variant has been detected in at least 7 independent occurrences with clinical features of a RASopathy (PS4; PMIDs: 17586837, 22420426, 28378436, 29037749, 25337068, 21387466, 21784453, 26918529, 21274610). In vitro functional studies provide some evidence that the p.Arg552Lys variant may impact protein function (PS3; PMID: 21784453). This residue has been defined as a PM1 hotspot by the RAS VCEP. 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). This variant was absent from large population studies (PM2; gnomAD,

http://gnomad.broadinstitute.org). Computational prediction tools and conservation analysis suggest that the p.Arg552Lys 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_VeryStrong, PS4, PS3, PM1_Strong, PM2, PP2, PP3.

Met criteria codes

PP2	✔	Variant is in SOS1
PP3	✔	REVEL score is 0.837
PM1_Strong	✔	This residue has been defined as a PM1 hotspot by the RAS VCEP. 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.
PS3	✔	Variant has shown signfiicant increase in ERK activation
PS4	✔	Kilinc et al. 2014: Variant was detected 12 year old boy with tooth anomalies, low set ears, bilateral proptosis, sparse eyebrows, epicanthal folds, hypertelorism, downslanting palpebral fissures, depressed nasal bridge, webbed neck, low posterior hairline, pectus excavatum, cubitus valgus, non palpable left testicle, myopia, scoliosis, diagnossi considered NS. Partners LMM: The variant has been identified in 6 affected patients with NS at this lab. Inheritance is unknown for these individuals. GeneDx:

The p.Arg552Lys variant was identified in 1 of the 19 participants in this study with NS. The patient also has hyperopic astigmatism, V pattern in esotropia. **PubMed:28378436**

YUWAND melanoma sample...3 variants were identified in the sample p.Phe694_Trp696del, PTPN11 p.Tyr279Cys, and SOS1 p.Arg552Lys **PubMed:26214590**

Variant was described to be a causative variant of melanoma and NS. No case evidence provided. **PubMed:27236105**

Sequenced 59 patients with NS, 17 with CFC, 5 with Costello, and 2 with NSML and identified the variant in 1 patient with NS. No detailed phenotypic information available. **PubMed:21784453**

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 2 sporadic cases with NS and 2 "fam.unknown" cases in this study. **PubMed:21387466**

The p.Arg552Lys variant was identified in 2 patients with NS/clincially related disorder. Detailed phenotypic information is not available **PubMed:29037749**

From March 2006 to March 2011, a total number of 62 patients from southern Tunisia attended the Department of Histology, Faculty of Medicine at the University of Sfax, for genetic counseling and chromosomal and/or molecular analysis for congenital PVS associated with or without another cardiac defect. All patients were ascertained through the Department of Cardiology, Hedi Chaker University Hospital of Sfax. The variant was identified in 8 year old female with NS, PVS, short stature, motor and speech delay, facial dysmorphisms **PubMed:25337068**

Variant was identified in an 8 year old female patient with NS **PubMed:21274610**

Patient 133-PRE is a prenatal patient with an AD/de novo heterozygous variant. The phenotypic information for this fetus was not recorded and therefore the clinical suspicion for NS cannot be used for PS4 or PM6/PS2 PubMed:30266093

2 newborn patients: Patient 35 and 36 one with cystic hygroma and increased NT and one with hydrops and pyelectasis with clinical suspicions of NS were identified with Tartaglia 2007 as references for pathogenicity of the variant. PubMed:26918529

PS2_Very Strong		✔	Patient 133-PRE is a prenatal patient with an AD/de novo heterozygous variant. The phenotypic information for this fetus was not recorded and therefore the clinical suspicion for NS cannot be used for PS4 or PM6/PS2 PubMed:30266093 The p.Arg552Lys variant was identified in a patient with Noonan syndrome with PVS + coronary dilatation and the variant was "further validated by Sanger sequencing using standard protocols and the analysis of proband's parents determined its de novo origin". PubMed:26686981

Not Met criteria codes

PP1		✖	One segregation was identified in Zenker et al. 2007 PMID: 17586837
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	Would be met but PS2_VS is applied so cannot be applied.

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The p.Arg552Lys variant was identified in a patient with Noonan syndrome with PVS + coronary dilatation and the variant was "further validated by Sanger sequencing using standard protocols and the analysis of proband's parents determined its de novo origin". PubMed:26686981

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
PM4		✖	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
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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