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Variant: NM_005633.3(SOS1):c.2673+14T>C

Version: 1.0

CA136107

45353 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 462195a4-85d8-4f09-bd70-1876d2f7ce13
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HGVS expressions

NM_005633.3:c.2673+14T>C
NM_005633.3(SOS1):c.2673+14T>C
NC_000002.12:g.39007017A>G
CM000664.2:g.39007017A>G
NC_000002.11:g.39234158A>G
CM000664.1:g.39234158A>G
NC_000002.10:g.39087662A>G
NG_007530.1:g.118447T>C
ENST00000685279.1:c.1440+14T>C
ENST00000689668.1:n.2680+14T>C
ENST00000690876.1:c.2562+14T>C
ENST00000691229.1:c.2442+14T>C
ENST00000692089.1:c.2562+14T>C
ENST00000692227.1:c.369+14T>C
ENST00000692620.1:c.*260+14T>C
ENST00000402219.8:c.2673+14T>C
ENST00000395038.6:c.2673+14T>C
ENST00000402219.6:c.2673+14T>C
ENST00000426016.5:c.2673+14T>C
ENST00000474390.1:n.469+14T>C
NM_001382394.1:c.2652+14T>C
NM_001382395.1:c.2673+14T>C
NM_005633.4:c.2673+14T>C

Benign

Met criteria codes 2

BP5 BA1

Not Met criteria codes 4

PP2 PM2 PM1 PS4

Evidence Links 1

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.2673+14T>C intronic variant in SOS1 is classified as benign because it has been identified in 0.34596% (lower bound of the 95% CI of 481/128770) of non-Finnish European chromosomes in gnomAD (BA1; https://gnomad.broadinstitute.org). This variant was observed in 1 individual with Noonan syndrome who also carried a pathogenic variant in SHOC2 sufficient to explain their clinical presentation (BP5; SCV000062214.5). ACMG/AMP Criteria applied: BA1, BP5.

Met criteria codes

BP5	✔	2 patients from LMM internal data had pathogenic variants in other genes (SHOC2:c.4A>G, classified as Path by RAS VCEP; PTPN11:c.179G>C, classified as Path by 5 submitters and well-studied in lit). Also observed by Lepri et al. Identified as a disease-unrelated SOS1 sequence variant in a patient. The RASopathy phenotype was not specified for the individual, but patients in the study had NS, CFCS, and CHDs. PubMed:21387466
BA1	✔	Identified in 0.34596% (lower bound of the 95% CI of 481/128770) of non-Finnish European chromosomes in gnomAD.

Not Met criteria codes

PP2	✖	SOS1 is not a missense-constrained gene in gnomAD.
PM2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	Not a coding variant for aa 420-500.
PS4	✖	Observed in multiple cases, but none were counted due to conflicting phenotypes. LMM: Identified in 6 probands -4yo white female tested for NS. Disease status listed as unknown. -3mo male tested for NS. Disease status listed as unknown. -Prenatal testing for NS. Disease status listed as unknown. Het. with PTPN11:c.124A>G. -Prenatal testing for NS. Disease status listed as unknown. -6mo Hispanic male with NS. Het. with SHOC2:c.4A>G (Pathogenic) -1yo white Male with NS. Het. with PTPN11:c.179G>C (Pathogenic) Lepri et al. 2011 (PMID: 21387466): -Identified as a disease-unrelated SOS1 sequence variant Prevention: Identified in 3 patients -9yo of European Caucasian/Native American/Pennsylvania Dutch descent presenting with lymphatic malformation (neck, cystic hygroma), splenic cysts, low ferritin, cognitive issues, disorder of auditory processing, retinopathy of prematurity, chronic abdominal pain, and muscle weakness (periodic limb disorder) -3mo Caucasian individual with webbed neck and undescended testicles -1mo of unknown ethnicity presenting with hydrops, down-slanting eyes, pectus, and broad thumbs Illumina: Identified in 8 individuals as part of the TruGenome Predisposition Screen test. ARUP: Identified in 3 cases. -1 case with possible Russell-Silver phenotype but lack of asymmetric growth and moderate developmental delay. No Noonan phenotype. -4yo Caucasian/Native American male with developmental delay, balance issues, hypospadias, adducted thumbs, and mild ptosis. Also reported to display hyperactivity, difficulty sleeping, frequent UTIs, and otitis media. -Additional case in fetal sample testing for Noonan panel. Ultrasound finding was large nuchal translucency. No family history of NS. GeneDx: Historical benign variant

Curation History

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