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Variant: NM_005633.3(SOS1):c.1654A>G (p.Arg552Gly)

CA235350

12871 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: b5a21ed5-8cbc-465c-8a14-9be1d1d54011
Approved on: 2017-04-03
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HGVS expressions

NM_005633.3(SOS1):c.1654A>G (p.Arg552Gly)
NM_005633.3:c.1654A>G
ENST00000395038.6:c.1654A>G
ENST00000402219.6:c.1654A>G
ENST00000426016.5:c.1654A>G
NC_000002.12:g.39022774T>C
CM000664.2:g.39022774T>C
NC_000002.11:g.39249915T>C
CM000664.1:g.39249915T>C
NC_000002.10:g.39103419T>C
NG_007530.1:g.102690A>G

Pathogenic

Met criteria codes 6

PP3 PP2 PS2_Very Strong PM2 PM1 PS3

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1654A>G (p.Arg552Gly) 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 17143282). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). In vitro functional studies provide some evidence that the p.Arg552Gly variant may impact protein function (PS3; PMID: 17143282). 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). Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of SOS1 (PM1; PMID 29493581). Computational prediction tools and conservation analysis suggest that the p.Arg552Gly 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): PP2, PP3, PM1, PM2, PS3, PS2_VeryStrong.

Met criteria codes

PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Arg552Gly variant may impact the protein (PP3).
PP2	✔	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).
PS2_Very Strong	✔	The c.1654A>G (p.Arg552Gly) 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 17143282).
PM2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✔	Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of SOS1 (PM1; PMID 29493581).
PS3	✔	In vitro functional studies provide some evidence that the p.Arg552Gly variant may impact protein function (PS3; PMID: 17143282).

Curation History

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