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Variant: NM_005633.3(SOS1):c.2536G>A (p.Glu846Lys)

CA261734

40706 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: f2a2e5e9-f8ba-43a4-9776-40b192ce87cf
Approved on: 2017-04-03
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HGVS expressions

NM_005633.3:c.2536G>A
NM_005633.3(SOS1):c.2536G>A (p.Glu846Lys)
ENST00000395038.6:c.2536G>A
ENST00000402219.6:c.2536G>A
ENST00000426016.5:c.2536G>A
ENST00000474390.1:n.332G>A
NC_000002.12:g.39007168C>T
CM000664.2:g.39007168C>T
NC_000002.11:g.39234309C>T
CM000664.1:g.39234309C>T
NC_000002.10:g.39087813C>T
NG_007530.1:g.118296G>A

Pathogenic

Met criteria codes 6

PP3 PP2 PM1 PM6 PM2 PS3

Not Met criteria codes 1

PS4

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.2536G>A (p.Glu846Lys) variant in SOS1 has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23673306). It has also been reported in a patient diagnosed with HCM (PMID 22555271). In vitro functional studies provide some evidence that the p.Glu846Lys variant may impact protein function (PS3; PMID 17143285). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). Computational prediction tools and conservation analysis suggest that the p.Glu846Lys 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). Furthermore, the variant is in a location that has been defined to be a mutational hotspot or

domain of SOS1 (PM1; PMID 21387466). 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, PM6, PS3.

Met criteria codes

PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Glu846Lys 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).
PM1	✔	Furthermore, the variant is in a location that has been defined to be a mutational hotspot or domain of SOS1 (PM1; PMID 21387466).
PM6	✔	The c.2536G>A (p.Glu846Lys) variant in SOS1 has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23673306). The c.2536G>A (p.Glu846Lys) variant in SOS1 has been reported in the literature as an unconfirmed de novo occurrence in a patient with clinical features of a RASopathy (PM6; PMID 23673306). PubMed:23673306
PM2	✔	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
PS3	✔	In vitro functional studies provide some evidence that the p.Glu846Lys variant may impact protein function (PS3; PMID 17143285) In vitro functional studies provide some evidence that the p.Glu846Lys variant may impact protein function (PS3; PMID 17143285) PubMed:17143285

Not Met criteria codes

PS4	✖	Variant has been reported in a patient diagnosed with HCM (PMID 22555271). PubMed:22555271

Curation History

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