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Variant: NM_005633.3(SOS1):c.806T>C (p.Met269Thr)

CA235344

40662 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 4536a40e-a4fc-474b-b83d-f63fa7e74a4a
Approved on: 2017-04-03
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HGVS expressions

NM_005633.3:c.806T>C
NM_005633.3(SOS1):c.806T>C (p.Met269Thr)
NC_000002.12:g.39051202A>G
CM000664.2:g.39051202A>G
NC_000002.11:g.39278343A>G
CM000664.1:g.39278343A>G
NC_000002.10:g.39131847A>G
NG_007530.1:g.74262T>C
ENST00000395038.6:c.806T>C
ENST00000402219.6:c.806T>C
ENST00000426016.5:c.806T>C
ENST00000461545.1:n.156T>C

Pathogenic

Met criteria codes 5

PM1 PM2 PS2_Very Strong PP3 PP2

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.806T>C (p.Met269Thr) variant in SOS1 has been reported in the literature in at least 2 unconfirmed and 1 confirmed de novo occurrences in patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17586837; 19953625, 20683980). It has also been reported as a confirmed de novo occurrence in a patient with clinical features of a RASoapthy (PMID: 20683980). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). The variant is in SOS1, which has been defined by the ClinGen RASopathy Expert Panel as a gene with low rate of benign missense with missense variants commonly being pathogenic (PP2; PMID 29493581). Computational prediction tools and conservation analysis suggest that the p.Met269Thr variant may impact the protein (PP3). 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). 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, PS2_VeryStrong.

Met criteria codes

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).
PM2	✔	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
PS2_Very Strong	✔	The c.806T>C (p.Met269Thr) variant in SOS1 has been reported in the literature in at least 2 unconfirmed and 1 confirmed de novo occurrences in patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17586837; 19953625, 20683980). The c.806T>C (p.Met269Thr) variant in SOS1 has been reported in the literature in at least 2 unconfirmed and 1 confirmed de novo occurrences in patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17586837; 19953625, 20683980). PubMed:17586837 The c.806T>C (p.Met269Thr) variant in SOS1 has been reported in the literature in at least 2 unconfirmed and 1 confirmed de novo occurrences in patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17586837; 19953625, 20683980). PubMed:19953625 The c.806T>C (p.Met269Thr) variant in SOS1 has been reported in the literature in at least 2 unconfirmed and 1 confirmed de novo occurrences in patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 17586837; 19953625, 20683980). PubMed:20683980
PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Met269Thr variant may impact the protein (PP3).
PP2	✔	The variant is in SOS1, which has been defined by the ClinGen RASopathy Expert Panel as a gene with low rate of benign missense with missense variants commonly being pathogenic (PP2; PMID 29493581).

Curation History

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