The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_005633.3(SOS1):c.39A>G (p.Glu13=)

Version: 1.2

CA1624896

282591 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 995211f5-9d35-4023-be4a-fe5f20bd1206
Approved on: 2019-11-04
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HGVS expressions

NM_005633.3:c.39A>G
NM_005633.3(SOS1):c.39A>G (p.Glu13=)
NC_000002.12:g.39120384T>C
CM000664.2:g.39120384T>C
NC_000002.11:g.39347525T>C
CM000664.1:g.39347525T>C
NC_000002.10:g.39201029T>C
NG_007530.1:g.5080A>G
ENST00000461545.2:n.66A>G
ENST00000689668.1:n.46A>G
ENST00000690679.1:c.187+3775A>G
ENST00000690876.1:c.39A>G
ENST00000691229.1:c.39A>G
ENST00000692089.1:c.39A>G
ENST00000402219.8:c.39A>G
ENST00000395038.6:c.39A>G
ENST00000402219.6:c.39A>G
ENST00000426016.5:c.39A>G
ENST00000451331.1:c.-85+3775A>G
NM_001382394.1:c.66+4280A>G
NM_001382395.1:c.39A>G
NM_005633.4:c.39A>G

Likely Benign

Met criteria codes 2
BP7 BP4

Not Met criteria codes 3
PM2 BP5 PS4

Evidence Links 0

Expert Panel
RASopathy VCEP

Criteria Specification Information
Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.39A>G (p.Glu13Glu) variant in SOS1 is classified as likely benign because it does not alter an amino acid residue, is not located within the splice consensus site, and computational splice prediction tools do not predict an impact on splicing (BP4, BP7). It has been identified in 0.004165% (5/120058) of non-Finnish European chromosomes in gnomAD (BS1 not met; https://gnomad.broadinstitute.org). This variant was observed in several individuals with varying clinical presentations that lacked clear associations with a RASopathy. In summary, this variant meets criteria to be classified as likely benign. ACMG/AMP criteria applied: BP4, BP7.

Met criteria codes

BP7	✔	Silent variant with no impact to splicing. Alamut indicates that this nucleotide is not highly conserved.
BP4	✔	Splicing is not predicted to be impacted in Alamut. REVEL score and conservation data not available for silent variants.

Not Met criteria codes

PM2	✖	Present in 0.004165% (5/120058) of non-Finnish European alleles in gnomAD.
BP5	✖	Internal data from Invitae describes a patient with ASD who also carried a pathogenic variant in PTPN11, but this individual did not have a clear diagnosis of a RASopathy.
PS4	✖	Internal data from 3 labs, but no individuals were counted towards PS4 without clear diagnoses of NS or other RASopathies. -EGL: Detected in one adult with short stature, hearing impairment, and developmental delay. This individual was found to have a variant that likely contributed to their short stature, but the complete phenotype could not be attributed to that variant. -Invitae: -One juvenile female with Tetralogy of Fallot -One juvenile male with atrial septal defect and a pathogenic variant in PTPN11 -Institut Universitaire d'Hematologie: 1 proband who also had VUS in RAF1 and SOS1

Curation History

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