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# *Variant: NM_005633.3(SOS1):c.322G>A (p.Glu108Lys)*

*CA261739*

*40649 (ClinVar)*

**Gene**: SOS1 (HGNC:6654)
**Condition**: Noonan syndrome (MONDO:0018997)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** 31e0095f-919b-4660-81cd-4f5bf83b5bcb
**Approved on**: 2017-04-03
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## *HGVS expressions*

**NM_005633.3(SOS1):c.322G>A (p.Glu108Lys)**
**NM_005633.3:c.322G>A**
ENST00000395038.6:c.322G>A
ENST00000402219.6:c.322G>A
ENST00000426016.5:c.322G>A
ENST00000451331.1:c.151G>A
NC_000002.12:g.39058696C>T
CM000664.2:g.39058696C>T
NC_000002.11:g.39285837C>T
CM000664.1:g.39285837C>T
NC_000002.10:g.39139341C>T
NG_007530.1:g.66768G>A

**Pathogenic**

**Met criteria codes** 6

PM6 PM2 PS4_Moderate PS2 PS3 PP2

Evidence Links 2

Expert Panel

RASopathy VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***RASopathy VCEP***

**The c.322G>A (p.Glu108Lys) variant in SOS1 has been reported as confirmed and unconfirmed occurrences in patients with clinical features of a RASopathy (PM6 and PS2; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2). The p.Glu108Lys variant has been identified in several independent occurrences in patients with clinical features of a RASopathy (PS4_Moderate; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2; PMID: 17143282; 23487764). In vitro functional studies provide some evidence that the p.Glu108Lys variant may impact protein function (PS3; PMID: 17143282, 23487764). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). 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). 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): PS2, PS3, PM6, PS4_Moderate, PM2, PP2.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM6** | ✔ | The c.322G>A (p.Glu108Lys) variant in SOS1 has been reported as confirmed and unconfirmed occurrences in patients with clinical features of a RASopathy (PM6 and PS2; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2). |
| **PM2** | ✔ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **PS4_Moderate** | ✔ | The p.Glu108Lys variant has been identified in several independent occurrences in patients with clinical features of a RASopathy (PS4_Moderate; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2; PMID: 17143282; 23487764).<br>The p.Glu108Lys variant has been identified in several independent occurrences in patients with clinical features of a RASopathy (PS4_Supporting; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2; PMID: 17143282; 23487764). PubMed:17143282<br>The p.Glu108Lys variant has been identified in several independent occurrences in patients with clinical features of a RASopathy (PS4_Supporting; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2; PMID: 17143282; 23487764). PubMed:23487764 |
| **PS2** | ✔ | The c.322G>A (p.Glu108Lys) variant in SOS1 has been reported as confirmed and unconfirmed occurrences in patients with clinical features of a RASopathy (PM6 and PS2; GeneDx, Partners LMM, APHP-Robert Debré Hospital internal data GTR Lab ID: 26957, 21766, 28338; ClinVar SCV000209088.9, SCV000062224.5, SCV000659144.2). |
| **PS3** | ✔ | In vitro functional studies provide some evidence that the p.Glu108Lys variant may impact protein function (PS3; PMID: 17143282, 23487764).<br>In vitro functional studies provide some evidence that the p.Glu108Lys variant may impact protein function (PS3; PMID: 17143282, 23487764). PubMed:17143282<br>In vitro functional studies provide some evidence that the p.Glu108Lys variant may impact protein function (PS3; PMID: 17143282, 23487764). PubMed:23487764 |
| **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). |

Curation History

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