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Variant: NM_005633.4(SOS1):c.1656G>C (p.Arg552Ser)

Version: 2.0

CA256580

12872 (ClinVar)

Gene: SOS1 (HGNC:6654)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: 7b69757f-5512-4640-93f6-c926e38cf7f9
Approved on: 2025/1/10
Published on: 2025/9/26

HGVS expressions

NM_005633.4(SOS1):c.1656G>C (p.Arg552Ser)
NM_005633.4:c.1656G>C
NC_000002.12:g.39022772C>G
CM000664.2:g.39022772C>G
NC_000002.11:g.39249913C>G
CM000664.1:g.39249913C>G
NC_000002.10:g.39103417C>G
NG_007530.1:g.102692G>C
ENST00000472480.2:n.1536G>C
ENST00000685279.1:c.423G>C
ENST00000688043.1:n.1877G>C
ENST00000689668.1:n.1663G>C
ENST00000690876.1:c.1545G>C
ENST00000691229.1:c.1545G>C
ENST00000692089.1:c.1545G>C
ENST00000692620.1:c.423G>C
ENST00000402219.8:c.1656G>C
ENST00000395038.6:c.1656G>C
ENST00000402219.6:c.1656G>C
ENST00000426016.5:c.1656G>C
NM_005633.3:c.1656G>C
NM_001382394.1:c.1635G>C
NM_001382395.1:c.1656G>C

Pathogenic

Met criteria codes 6

PS2_Very Strong | PM5_Strong | PM2_Supporting | PS3_Supporting | PS4 | PP3

Not Met criteria codes 20

PM6 | PM1 | PM3 | PM4 | PVS1 | BS1 | BS4 | BS3 | BS2 | BP5 | BP7 | BP4 | BP3 | BP1 | BP2 | BA1 | PS1 | PP1 | PP2 | PP4

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen RASopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SOS1 Version 2.3.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

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Evidence submitted by expert panel

RASopathy VCEP

The NM_005633.4:c.1656G>C variant in SOS1 is a missense variant predicted to cause substitution of arginine by serine at amino acid 552 (p.Arg552Ser). This variant was absent from gnomAD v2.1.1 (PM2_Supporting). The computational prediction tool REVEL gives a score of 0.863, suggesting that the p.Arg552Ser variant may impact protein function (PP3). Five different (likely) pathogenic variants at this residue (Arg552Gly, Arg552Lys, Arg552Met, Arg552Thr, Arg552Trp) have been identified in several patients with RASopathies (PM5_Strong). This variant has been reported in at least 8 patients with clinical features of a RASopathy, of which 2 were reported as confirmed de novo occurrences and 1 was assumed to be de novo (PS4, PS2_VeryStrong; PMIDs:17143282, 19352411, 18651097, 18925667, 1902079). In vitro functional studies showed that the p.Arg552Ser variant led to increased ERK1/2 phosphorylation (PS3_Supporting; PMID: 27304678). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathy based on the ACMG/AMP criteria as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS2_VeryStrong, PS4, PM5_Strong, PS3_Supporting PM2_Supporting, PP3 (Specification Version 2.3, 1/10/2025)

Met criteria codes

PS2_Very Strong ✔

The p.Arg552Ser variant was identified in 2 de novo occurrences in patients with Noonan syndrome. Variants were absent from both parents and paternity was confirmed for each. It was also identified in another proband who was assumed to be de novo.

The p.Arg552Ser variant was identified in 2 de novo occurrences in patients with Noonan syndrome. Variants were absent from both parents and paternity was confirmed for each. PubMed:17143282

PM5_Strong ✔

This residue has been identified as a hotspot with several likely pathogenic/pathogenic variants at this codon (Arg552Gly, Arg552Lys, Arg552Met, Arg552Thr, Arg552Trp).

PM2_Supporting ✔

This variant is absent from gnomAD v2.1.1 (PM2_supporting).

PS3_Supporting ✔

The variant increased p-ERK signaling in transfected HEK293T cells (PMID 27304678)

Transfected wild-type and mutant SOS1 constructs into HEK293T cells and measured the effect on basal levels of phosphorylated ERK1/2. Found that the p.R552S variant significantly increased p-ERK signaling relative to WT (p = 0.0039). This meets criteria for PS3. PubMed:27304678

PS4 ✔

This variant has been reported in at least 8 patients with clinical features of a RASopathy occurrences (PMIDs:17143282, 19352411, 18651097, 18925667, 1902079).

This study sequenced 96/134 patients with clinical features fitting the RASopathy spectrum evaluated in their first year of life.This variant was identified in one patient with NS. PubMed:22190897
This study sequenced 19 patients with NS and the p.Arg552Ser varinat was identified in Patient 18. There was no indication of which c.DNA change was identified in this patient. PubMed:28378436
59 patients with NS, 17 with cardiofaciocutaneous syndrome, 5 with Costello syndrome, and 2 with LEOPARD syndrome were sequenced and 2 of the patients had p.Arg552Ser variants. These are likely the Korean patients described in the Ko paper as these patients are also from Korea. PubMed:21784453

Identified the p.Arg552Ser variant in a patient with NS but no additional clinical information is available. It is not stated which c. change this is. Additionally it is unclear how many patients were identified with this variant. PubMed:22465605

This case report of a 14 year old girl with chronic pain in NS identified the p.Arg552Ser variant. The c.DNA change was not reported. PubMed:26297936

In this paper, cancer samples were sequenced and they identified the p.Arg552Ser variant. They identified both the c.1656G>C and c.1656G>T variant, each in 1 occurrence. PubMed:29625050

Four cohorts were included in this study...143 clinically well-characterized patients with NS of European/Italian ancestry, patients from the Sarkozy 2009 study, (N= 358) anonymous samples from individuals with phenotypes suggestive of NS from commercial DNA diagnostic testing, finally a cohort of 59 subjects with nonsyndromic CHD's. This was a large study of patients with clinical features of a RASopathy that has been described elsewhere. This study describes c.1656G>C (p.Arg552Ser) in 2 sporadic, 7 fam unknown cases PubMed:21387466

Case 4, an 82 year old man with late-onset HCM was found to carry the pathogenic c.1656G>C (p.Arg552Ser). The allelic fraction for the variant was 24% via NGS suggestive of mosaicism. Sanger sequencing was consistent. This mosaicism is likely the reason for the nonsyndromic HCM presentation. PubMed:29696744

This study sequenced 42 patients from the Outpatient Clinic of the Genetics Unit of the Children's Hospital and reported 2 patients with the p.Arg552Ser variants. The cohort is considered a NS, NSML and CFC cohort, but detailed phenotypic information and c.DNA change is not provided. Cannot count. PubMed:22488759

Sequenced 33 NS patients and Identified the c.1656G>C (p.Arg552Ser) variant in one patient. The variant was inherited from an affected mother. The patient was a female with typical face, hypertelorism, downslanting palpebral fissures , ptosis, curly hair, sparse eyebrows, webbed/short neck, pectus deformity, keratosis, Navl/lentigines, short stature, easy bruising, heart defect, pulmonary stenosis, aberrant ECG, left-axis deviation PubMed:23885229

Sequenced 97 Noonan syndrome patients and identified the p.Arg552Ser in one patient who did not have hearing loss in this NS/HL cohort. PubMed:25862627

The p.Arg552Ser variant was identified in 2 de novo occurrences in patients with Noonan syndrome. Variants were absent from both parents and paternity was confirmed for each. PubMed:17143282

2 patients with variant. Patient 1: Stenosis of the pulmonary valve, diagnosed in early infancy, typical features of NS. Karyotype was 46, XY, inv(9) (p11q13). Bilateral radiolucent cysts of the mandible, normal stature and no learning difficulties. Patient had the p.Arg552Ser variant. Patient 3: Stenosis of the pulmonary artery and atrial septal defect. Clinical features typical for NS. PVS of the left ankle diagnosed at 12 years, delaryed puberty, left cryptorchidism, no learning disabilities. No involvement of the jaws. The p.Arg552Ser variant was present in this individual with unknown inheritance. PubMed:19352411

The p.Arg552Ser variant was identified in this NS patient with pigmented villonodular synovitis. The c.DNA change is not described in this case study. Therefore this occurrence cannot be counted. PubMed:18925667

Of the 59 Korean NS patients sequenced, 2 of the patients in this study had the c.1656G>C p.R552S variants. PubMed:19020799

PP3 ✔ REVEL score 0.863

Not Met criteria codes

PM6 ✖ PM6 cannot be applied because PS2_VS has been applied.

The p.Arg552Ser variant was identified in 2 de novo occurrences in patients with Noonan syndrome. Variants were absent from both parents and paternity was confirmed for each. PubMed:17143282

PM1 ✖

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	This variant is absent from gnomAD v2.1.1 (PM2_supporting).
BS4	✖	Sequenced 33 NS patients and Identified the c.1656G>C (p.Arg552Ser) variant in one patient. The variant was inherited from an affected mother. The patient was a female with typical face, hypertelorism, downslanting palpebral fissures , ptosis, curly hair, sparse eyebrows, webbed/short neck, pectus deformity, keratosis, Navl/lentigines, short stature, easy bruising, heart defect, pulmonary stenosis, aberrant ECG, left-axis deviation PubMed:23885229
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	This variant is absent from gnomAD v2.1.1 (PM2_supporting).

PS1		✖	This variant was used to support the pathogenicity of the c.1656G>T transition in SOS1.
PP1		✖	Variant segregated in one mother child duo (PMID: 23885229). Sequenced 33 NS patients and Identified the c.1656G>C (p.Arg552Ser) variant in one patient. The variant was inherited from an affected mother. The patient was a female with typical face, hypertelorism, downslanting palpebral fissures , ptosis, curly hair, sparse eyebrows, webbed/short neck, pectus deformity, keratosis, Navl/lentigines, short stature, easy bruising, heart defect, pulmonary stenosis, aberrant ECG, left-axis deviation PubMed:23885229
PP2		✖	The Z-score for missense variants in SOS1 is 2.34 (PP2 not met).
PP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 2 of 2 rows

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