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Variant: NM_005343.3(HRAS):c.34G>A (p.Gly12Ser)

CA122549

12602 (ClinVar)

Gene: LRRC56 (HGNC:3265)
Condition: Costello syndrome (MONDO:0009026)
Inheritance Mode: Autosomal dominant inheritance
UUID: 51947641-2e77-498f-93d6-ca73b8e343de
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_005343.3:c.34G>A
NM_005343.3(HRAS):c.34G>A (p.Gly12Ser)
NC_000011.10:g.534289C>T
CM000673.2:g.534289C>T
NC_000011.9:g.534289C>T
CM000673.1:g.534289C>T
NC_000011.8:g.524289C>T
NG_007666.1:g.6262G>A
NM_001130442.1:c.34G>A
NM_005343.2:c.34G>A
NM_176795.3:c.34G>A
NM_001130442.2:c.34G>A
NM_001318054.1:c.-286G>A
NM_176795.4:c.34G>A
NM_005343.4:c.34G>A
ENST00000311189.7:c.34G>A
ENST00000397594.5:c.34G>A
ENST00000397596.6:c.34G>A
ENST00000417302.5:c.34G>A
ENST00000451590.5:c.34G>A
ENST00000468682.2:n.522G>A
ENST00000482021.1:n.157G>A
ENST00000493230.5:c.34G>A

Pathogenic

Met criteria codes 7

PS4 PS3 PP3 PP2 PM2 PM1 PS2_Very Strong

Evidence Links 15

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404). The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). In vitro functional studies provide some evidence that the p.Gly12Ser variant may impact protein function (PS3; PMID: 17412879). Computational prediction tools and conservation analysis suggest that the p.Gly12Ser 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 HRAS (PM1; PMID 29493581). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). The variant is located in the HRAS 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_VeryStrong, PS4, PS3, PM1, PM2, PP2, PP3.

Met criteria codes

PS4

The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863).

The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). PubMed:19206176

The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). PubMed:19371735

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The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). PubMed:16372351

The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). PubMed:16969868

The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). PubMed:16835863

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The p.Gly12Ser variant has been identified in >5 independent occurrences in patients with clinical features of a RASopathy (PS4; PMID: 20660566, 16372351, 16329078, 16969868, 18039947, 19371735, 19206176, 16835863). PubMed:18039947

PS3

In vitro functional studies provide some evidence that the p.Gly12Ser variant may impact protein function (PS3; PMID: 17412879).

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PP3

Computational prediction tools and conservation analysis suggest that the p.Gly12Ser variant may impact the protein (PP3).

PP2	✔	The variant is located in the HRAS 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).
PM2	✔	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
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 HRAS (PM1; PMID 29493581) 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 HRAS (PM1; PMID 29493581) **PubMed:29493581**
PS2_Very Strong	✔	The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) **PubMed:17054105** The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) **PubMed:16443854** The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) **PubMed:19669404** The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) **PubMed:16170316** The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) **PubMed:16881968** The c.34G>A (p.Gly12Ser) variant in HRAS has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStrong; PMID 16170316, 16835863, 16443854, 16835863, 16881968, 17054105, 19669404) **PubMed:16835863**

Curation History

Showing 1 to 1 of 1 rows

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