Variant: NM_005343.3(HRAS):c.37G>T (p.Gly13Cys)

CA295247

12606 (ClinVar)

Gene: LRRC56 (HGNC:3265)
Condition: Noonan syndrome (MONDO:0018997)
Inheritance Mode: Autosomal dominant inheritance
UUID: 77fd6395-3146-46f0-86ca-08fb626eb660
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HGVS expressions

NM_005343.3:c.37G>T
NM_005343.3(HRAS):c.37G>T (p.Gly13Cys)
NM_001130442.1:c.37G>T
NM_005343.2:c.37G>T
NM_176795.3:c.37G>T
NM_001130442.2:c.37G>T
NM_001318054.1:c.-283G>T
NM_176795.4:c.37G>T
NM_005343.4:c.37G>T
ENST00000311189.7:c.37G>T
ENST00000397594.5:c.37G>T
ENST00000397596.6:c.37G>T
ENST00000417302.5:c.37G>T
ENST00000451590.5:c.37G>T
ENST00000468682.2:n.525G>T
ENST00000482021.1:n.160G>T
ENST00000493230.5:c.37G>T
NC_000011.10:g.534286C>A
CM000673.2:g.534286C>A
NC_000011.9:g.534286C>A
CM000673.1:g.534286C>A
NC_000011.8:g.524286C>A
NG_007666.1:g.6265G>T

Pathogenic

Met criteria codes 6

PS4_Moderate | PS2_Very Strong | PP3 | PP2 | PM1 | PM2

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.37G>T (p.Gly13Cys) 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 21438134, 16329078). The p.Gly13Cys variant has been identified in at least 3 other independent occurrence in patients with clinical features of a RASopathy (PS4_Moderate; PMID: 16372351). 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). Computational prediction tools and conservation analysis suggest that the p.Gly13Cys 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). 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, PS4_Moderate, PS2_VeryStrong.

Met criteria codes

PS4_Moderate	✔	The p.Gly13Cys variant has been identified in at least 3 other independent occurrence in patients with clinical features of a RASopathy (PS4_Moderate; PMID: 16372351).
PS2_Very Strong	✔	The c.37G>T (p.Gly13Cys) 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 21438134, 16329078). The c.37G>T (p.Gly13Cys) 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 21438134, 16329078). PubMed:16329078 The c.37G>T (p.Gly13Cys) 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 21438134, 16329078). PubMed:21438134
PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Gly13Cys 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).
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). PubMed:29493581
PM2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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