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Variant: NM_004985.4(KRAS):c.178G>C (p.Gly60Arg)

CA273416

12586 (ClinVar)

Gene: KRAS (HGNC:3845)
Condition: cardiofaciocutaneous syndrome (MONDO:0015280)
Inheritance Mode: Autosomal dominant inheritance
UUID: a8c6153e-d737-4b86-8d68-caf8ddd418fd
Approved on: 2017-04-03
Published on: 2018-12-10

HGVS expressions

NM_004985.4:c.178G>C
NM_004985.4(KRAS):c.178G>C (p.Gly60Arg)
NC_000012.12:g.25227346C>G
CM000674.2:g.25227346C>G
NC_000012.11:g.25380280C>G
CM000674.1:g.25380280C>G
NC_000012.10:g.25271547C>G
NG_007524.1:g.28575G>C
NM_033360.3:c.178G>C
ENST00000256078.8:c.178G>C
ENST00000311936.7:c.178G>C
ENST00000557334.5:c.112-17435G>C

Pathogenic

Met criteria codes 6

PM2 PM1 PS3 PM6_Strong PP3 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.178G>C (p.Gly60Arg) variant in KRAS has been reported in the literature as a de novo occurrence in 2 patients with clinical features of a RASopathy (PM6_Strong; PMID 16474404, 20949621). In vitro functional studies provide some evidence that the p.Gly60Arg variant may impact protein function (PS3; PMID 20949621). This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org). The variant is in KRAS, which has been defined by the ClinGen RASopathy Expert Panel as a gene with low rate of benign missense with missense variants commonly being pathogenic (PP2; 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 KRAS (PM1; PMID 29493581). Computational prediction tools and conservation analysis suggest that the p.Gly60Arg variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for RASopathies in an autosomal dominant manner. ACMG/AMP criteria applied: PM6_Strong, PS3, PM2, PM1, PP3, PP2.

Met criteria codes

PM2	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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 KRAS (PM1; PMID 29493581).
PS3	✔	In vitro functional studies provide some evidence that the p.Gly60Arg variant may impact protein function (PS3; PMID 20949621). In vitro functional studies provide some evidence that the p.Gly60Arg variant may impact protein function (PS3; PMID 20949621). PubMed:20949621
PM6_Strong	✔	The c.178G>C (p.Gly60Arg) variant in KRAS has been reported in the literature as a de novo occurrence in 2 patients with clinical features of a RASopathy (PM6_Strong; PMID 16474404, 20949621). The c.178G>C (p.Gly60Arg) variant in KRAS has been reported in the literature as a de novo occurrence in 2 patients with clinical features of a RASopathy (PM6_Strong; PMID 16474404, 20949621). PubMed:20949621 The c.178G>C (p.Gly60Arg) variant in KRAS has been reported in the literature as a de novo occurrence in 2 patients with clinical features of a RASopathy (PM6_Strong; PMID 16474404, 20949621). PubMed:16474404
PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Gly60Arg variant may impact the protein (PP3).
PP2	✔	The variant is in KRAS, which has been defined by the ClinGen RASopathy Expert Panel as a gene with low rate of benign missense with missense variants commonly being pathogenic (PP2; PMID 29493581)

Curation History

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