

Variant: NM_002755.3(MAP2K1):c.389A>G (p.Tyr130Cys)

CA280036 [↗](#)

13351 (ClinVar) [↗](#)

Gene: MAP2K1 ([HGNC:5604](#))

Condition: cardiofaciocutaneous syndrome ([MONDO:0015280](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 1eaf4dad-ab0c-49ae-8548-22bad4210249

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HGVS expressions

NM_002755.3(MAP2K1):c.389A>G (p.Tyr130Cys)

NM_002755.3:c.389A>G

ENST00000307102.9:c.389A>G

ENST00000425818.2:n.900A>G

NC_000015.10:g.66436843A>G

CM000677.2:g.66436843A>G

NC_000015.9:g.66729181A>G

CM000677.1:g.66729181A>G

NC_000015.8:g.64516235A>G

NG_008305.1:g.54971A>G

Pathogenic

Met criteria codes **6**

PS3 PP3 PP2 PM2 PS2_Very

Strong PM1

Evidence Links **6**

Expert Panel

[RASopathy VCEP](#) [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

RASopathy VCEP

The c.389A>G (p.Tyr130Cys) variant in MAP2K1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VeryStong; PMID 16439621, 17551924, 18042262). In vitro functional studies provide some evidence that the p.Tyr130Cys variant may impact protein function (PS3; PMID 18413255, 23093928, 17981815). This variant was absent from large population studies (PM2; ExAC, <http://exac.broadinstitute.org>). The variant is located in the MAP2K1 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). 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 MAP2K1 (PM1; PMID 29493581). Computational prediction tools and conservation analysis suggest that the p.Tyr130Cys variant may impact the protein (PP3). 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, PP3, PS3, PM2, PP2, PM1.

Met criteria codes

PS3			In vitro functional studies provide some evidence that the p.Tyr130Cys variant may impact protein function (PS3; PMID 18413255, 23093928, 17981815). In vitro functional studies provide some evidence that the p.Tyr130Cys variant may impact protein function (PS3; PMID 18413255, 23093928, 17981815). PubMed:18413255  In vitro functional studies provide some evidence that the p.Tyr130Cys variant may impact protein function (PS3; PMID 18413255, 23093928, 17981815). PubMed:17981815  In vitro functional studies provide some evidence that the p.Tyr130Cys variant may impact protein function (PS3; PMID 18413255, 23093928, 17981815). PubMed:23093928 
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			The variant is in MAP2K1, 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)
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2_Very Strong			The p.Tyr130Cys variant in MAP2K1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VS; PMID 16439621, 17551924, 18042262). The p.Tyr130Cys variant in MAP2K1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VS; PMID 16439621, 17551924, 18042262). PubMed:16439621  The p.Tyr130Cys variant in MAP2K1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VS; PMID 16439621, 17551924, 18042262). PubMed:18042262  The p.Tyr130Cys variant in MAP2K1 has been reported as a confirmed de novo occurrence in at least 2 patients with clinical features of a RASopathy (PS2_VS; PMID 16439621, 17551924, 18042262). PubMed:17551924 
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 MAP2K1 (PM1; PMID 29493581)

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