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Variant: NM_002755.3(MAP2K1):c.388T>C (p.Tyr130His)

CA279999

40747 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: cardiofaciocutaneous syndrome (MONDO:0015280)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9f86afbc-b31d-472c-ac5d-ee0799f21c9c
Approved on: 2017-05-09
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HGVS expressions

NM_002755.3(MAP2K1):c.388T>C (p.Tyr130His)
NM_002755.3:c.388T>C
NM_002755.4:c.388T>C
ENST00000307102.9:c.388T>C
ENST00000425818.2:n.899T>C
NC_000015.10:g.66436842T>C
CM000677.2:g.66436842T>C
NC_000015.9:g.66729180T>C
CM000677.1:g.66729180T>C
NC_000015.8:g.64516234T>C
NG_008305.1:g.54970T>C

Pathogenic

Met criteria codes 6

PP3 PP2 PM6_Strong PM2 PM5 PS4_Supporting

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.388T>C (p.Tyr130His) variant in MAP2K1 has been reported as an unconfirmed de novo occurrence in two probands with clinical features of a RASopathy (PM6_Strong; PMID: 1915617, Ambry Genetics internal data, ClinVar SCV000740998.1). One of these patients had a clinical diagnosis of cardiofaciocutaneous syndrome (PS4_Supporting). This variant was absent from large population studies (PM2; gnomad.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). 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 not applied; PMID 29493581). Moreover, a different pathogenic missense variant has been previously identified at this codon of MAP2K1 which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 13351). Computational prediction tools and conservation analysis suggest that the p.Tyr130His 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): PS4_Supporting, PM6_Strong, PM5, PM2, PP2, PP3.

Met criteria codes

PP3	✔	Computational prediction tools and conservation analysis suggest that the p.Tyr130His variant may impact the protein (PP3).
PP2	✔	The variant is in MAP2K1, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants with missense variants commonly being pathogenic (PP2; PMID 29493581)
PM6_Strong	✔	The p.Tyr130His variant in MAP2K1 has been reported in the literature as a de novo occurrence (without maternity/paternity confirmed) in 2 patients with clinical features of a RASopathy (PM6_Strong; PMID 19156172, Ambry Genetics internal data, ClinVar SCV000740998.1).
PM2	✔	Absent from both versions of gnomAD.
PM5	✔	A different pathogenic missense variant has been previously identified at this codon of MAP2K1 which may indicate that this residue is critical to the function of the protein (PM5; ClinVar 13351).
PS4_Supporting	✔	Observed in 1 proband with a diagnosis of CFC (Ambry Genetics internal data, ClinVar SCV000740998.1)

Curation History

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