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Variant: NM_002755.3(MAP2K1):c.364A>G (p.Asn122Asp)

Version: 1.0

CA10576999

228273 (ClinVar)

Gene: MAP2K1 (HGNC:5604)
Condition: RASopathy (MONDO:0021060)
Inheritance Mode: Autosomal dominant inheritance
UUID: e13f1eb9-0fbc-4e6c-96cf-d06a0b166fca
Approved on: 2020/3/16
Published on: 2020/3/24

HGVS expressions

NM_002755.3:c.364A>G
NM_002755.3(MAP2K1):c.364A>G (p.Asn122Asp)
NC_000015.10:g.66436818A>G
CM000677.2:g.66436818A>G
NC_000015.9:g.66729156A>G
CM000677.1:g.66729156A>G
NC_000015.8:g.64516210A>G
NG_008305.1:g.54946A>G
ENST00000684779.1:c.298A>G
ENST00000685172.1:c.364A>G
ENST00000685763.1:c.291+1581A>G
ENST00000686347.1:c.364A>G
ENST00000687191.1:n.800A>G
ENST00000689951.1:c.364A>G
ENST00000691077.1:c.364A>G
ENST00000691576.1:c.364A>G
ENST00000691937.1:c.364A>G
ENST00000692487.1:c.364A>G
ENST00000692683.1:c.298A>G
ENST00000693150.1:c.298A>G
ENST00000307102.10:c.364A>G
ENST00000307102.9:c.364A>G
ENST00000425818.2:n.875A>G
NM_002755.4:c.364A>G

Pathogenic

Met criteria codes 4

PP2 PS4_Supporting PM2 PS2_Very Strong

Evidence Links 0

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.364A>G (p.Asn122Asp) variant in MAP2K1 was absent from gnomAD (PM2). It has been observed in 3 probands with clinical features of a RASopathy, including 1 de novo occurrence with maternity and paternity confirmed and 2 assumed de novo occurrences (PM2_VS; SCV000271240.2; Otto-von-Guericke-Universität Magdeburg internal communication; Invitae internal data, SCV000947966.1). Of these patients, 2 received a clinical diagnosis of either Noonan syndrome or cardiofaciocutaneous syndrome (PS4_Supporting). Of note, this variant was observed in 1 proband without clinical information who inherited it from a parent with unknown clinical status (GeneDx internal data). The c.364A>G (p.Asm122Asp) variant is located in MAP2K1, 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 autosomal dominant RASopathy based on RASopathy-specific ACMG/AMP criteria (PMID:29493581): PS2_VS, PS4_Supporting, PM2, PP2.

Met criteria codes

PP2	✔	MAP2K1 is a missense-constrained gene.
PS4_Supporting	✔	Otto-von-Guericke-Universität Magdeburg internal communication: Observed in a child with CFC, assumed de novo without parentage confirmed LMM: 6 week old male with features of NS de novo w/o parentage confirmation (SCV000271240.2)
PM2	✔	Absent from gnomAD.
PS2_Very Strong	✔	This variant was observed as an assumed de novo occurrence without parentage confirmed in 2 cases (LMM internal data, SCV000271240.2; Otto-von-Guericke-Universität Magdeburg internal communication). It was also observed de novo in one case with features of a RASopathy with confirmed paternity and maternity (SCV000947966.1).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_002755.3(MAP2K1):c.364A>G (p.A...	Pathogenic	RASopathy	2020-03-24	1.0	-	MAP2K1

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