

Variant: NM_002880.4(RAF1):c.1837C>G (p.Leu613Val)

CA257066 [↗](#)

13960 (ClinVar) [↗](#)

Gene: RAF1 ([HGNC:5894](#))

Condition: RASopathy ([MONDO:0021060](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: f8f03fe0-c539-40c8-ad23-64451f155a8c

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HGVS expressions

NM_002880.4:c.1837C>G

NM_002880.4(RAF1):c.1837C>G (p.Leu613Val)

NC_000003.12:g.12584624G>C

CM000665.2:g.12584624G>C

NC_000003.11:g.12626123G>C

CM000665.1:g.12626123G>C

NC_000003.10:g.12601123G>C

NG_007467.1:g.84556C>G

ENST00000423275.6:c.*1502C>G

ENST00000432427.3:c.1154C>G

ENST00000460610.2:n.6149C>G

ENST00000471449.2:n.647C>G

ENST00000475353.2:n.4117C>G

ENST00000684903.1:c.*1514C>G

ENST00000685348.1:c.*1548C>G

ENST00000685437.1:c.1738C>G

ENST00000685653.1:c.1837C>G

ENST00000685697.1:n.2572C>G

ENST00000685738.1:c.*801C>G

ENST00000686409.1:n.5246C>G

ENST00000686455.1:n.4558C>G

ENST00000686762.1:c.*396C>G

ENST00000687257.1:n.4291C>G

ENST00000687326.1:c.*3129C>G

ENST00000687505.1:n.1955C>G

ENST00000687923.1:c.1726C>G

ENST00000688269.1:n.2433C>G

ENST00000688444.1:n.3954C>G

ENST00000688543.1:c.1738C>G

ENST00000688625.1:c.*3206C>G

ENST00000688803.1:n.3265C>G

ENST00000689097.1:c.*1514C>G

ENST00000689389.1:c.1660C>G

ENST00000689418.1:c.*3732C>G

ENST00000689540.1:n.4205C>G

ENST00000689876.1:c.*386C>G

ENST00000689914.1:c.*771C>G

ENST00000690397.1:c.1726C>G
ENST00000690460.1:c.1825C>G
ENST00000690585.1:c.563C>G
ENST00000690625.1:n.2873C>G
ENST00000691396.1:c.*1709C>G
ENST00000691643.1:n.2890C>G
ENST00000691724.1:c.*794C>G
ENST00000691779.1:c.*1415C>G
ENST00000691888.1:c.711C>G
ENST00000691899.1:c.1837C>G
ENST00000692069.1:n.4761C>G
ENST00000692093.1:c.1738C>G
ENST00000692311.1:n.2661C>G
ENST00000692558.1:n.4420C>G
ENST00000692773.1:c.*1574C>G
ENST00000692830.1:c.*1582C>G
ENST00000693312.1:c.1612C>G
ENST00000693664.1:c.*288C>G
ENST00000693705.1:c.*1216C>G
ENST00000251849.9:c.1837C>G
ENST00000442415.7:c.1897C>G
ENST00000676541.1:c.*2371G>C
ENST00000677142.1:c.*2371G>C
ENST00000677816.1:c.*926G>C
ENST00000677941.1:n.2434G>C
ENST00000251849.8:c.1837C>G
ENST00000423275.5:c.*1514C>G
ENST00000432427.2:c.1474C>G
ENST00000442415.6:c.1897C>G
ENST00000471449.1:n.526C>G
NM_002880.3:c.1837C>G
NM_001354689.1:c.1897C>G
NM_001354690.1:c.1837C>G
NM_001354691.1:c.1594C>G
NM_001354692.1:c.1594C>G
NM_001354693.1:c.1738C>G
NM_001354694.1:c.1654C>G
NM_001354695.1:c.1495C>G
NR_148940.1:n.2365C>G
NR_148941.1:n.2311C>G
NR_148942.1:n.2250C>G
NM_001354689.3:c.1897C>G
NM_001354690.2:c.1837C>G
NM_001354691.2:c.1594C>G
NM_001354692.2:c.1594C>G
NM_001354693.2:c.1738C>G
NM_001354694.2:c.1654C>G
NM_001354695.2:c.1495C>G
NR_148940.2:n.2281C>G
NR_148941.2:n.2227C>G
NR_148942.2:n.2166C>G
NM_001354690.3:c.1837C>G

NM_001354691.3:c.1594C>G
NM_001354692.3:c.1594C>G
NM_001354693.3:c.1738C>G
NM_001354694.3:c.1654C>G
NM_001354695.3:c.1495C>G
NR_148940.3:n.2281C>G
NR_148941.3:n.2227C>G
NR_148942.3:n.2166C>G

Pathogenic

Met criteria codes 4

PS3_Moderate PS4 PM2_Supporting
PS2_Very Strong

Evidence Links 3

Expert Panel

RASopathy VCEP

Criteria Specification Information

Criteria Specification: ClinGen RASopathy Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines for RAF1 Version 2.3.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

RASopathy VCEP

The c.1837C>G (p.Leu613Val) variant in the RAF1 gene is a missense variant predicted to cause substitution of leucine by valine at amino acid 613. This variant is absent from gnomAD v2 (PM2_Supporting). The variant has been reported in at least one confirmed de novo case in an individual with clinical features of a RASopathy (PS2_VeryStrong; PMID:17603483), and its prevalence in affecteds is statistically increased over controls (PS4). In vitro functional studies also provide some evidence that the p.Leu613Val variant may impact protein function (PS3; PMID: 7603482, 17603483, 22826437). In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant RASopathies based on ACMG/AMP criteria applied, as specified by the ClinGen RASopathy Variant Curation Expert Panel: PS2_VeryStrong, PS4, PS3_Moderate, PM2_Supporting. (Specification Version 2.3, 12/3/2024)

Met criteria codes

PS3_Moderate



In vitro functional studies provide some evidence that the p.Leu613Val variant may impact protein function (PMID: 7603482, 17603483, 22826437).

In vitro functional studies provide some evidence that the p.Leu613Val variant may impact protein function (PS3; 17603482, 17603483, 22826437). [PubMed:17603483](#)

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In vitro functional studies provide some evidence that the p.Leu613Val variant may impact protein function (PS3; 17603482, 17603483, 22826437). [PubMed:22826437](#)

PS4



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM2_Supporting			This variant is absent from gnomAD v4
PS2_Very Strong			The c.1837C>G (p.Leu613Val) variant in RAF1 has been reported in at least one confirmed de novo case in an individual with clinical features of a RASopathy (PMID 17603483).

Curation History 		
		
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