

*Variant: NM\_000277.1:c.694C>G*

CA16020842 [↗](#)

619160 (ClinVar) [↗](#)

**Gene:** PAH ([HGNC:5053](#))

**Condition:** phenylketonuria ([MONDO:0009861](#))

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 2d2e4a9f-fe71-4d44-a8d9-cc64cd71145d

**Approved on:** 2018-12-10

**Published on:** 2018-12-10

### *HGVS expressions*

**NM\_000277.1:c.694C>G**

NC\_000012.12:g.102855148G>C

CM000674.2:g.102855148G>C

NC\_000012.11:g.103248926G>C

CM000674.1:g.103248926G>C

NC\_000012.10:g.101773056G>C

NG\_008690.1:g.67455C>G

NG\_008690.2:g.108263C>G

NM\_000277.2:c.694C>G

NM\_001354304.1:c.694C>G

NM\_000277.3:c.694C>G

ENST00000307000.7:c.679C>G

ENST00000549111.5:n.790C>G

ENST00000553106.5:c.694C>G

**Likely Pathogenic**

**Met criteria codes** **2**

**PS3**

**PM2**

**Not Met criteria codes** **1**

**PP3**

**Evidence Links** **1**

**Expert Panel**

**Phenylketonuria VCEP** [↗](#)

**Criteria Specification Information** **!**

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

Evidence submitted by expert panel

#### ***Phenylketonuria VCEP***

The c.694C>G (p.Gln232Glu) variant in PAH has not been reported in the literature in individuals with PKU. It has been co-expressed with p.E178G and showed 55.0% enzyme activity. PMID: 26803807. BioPKU reports a 42% enzyme activity for this variant (PS3; PMID: 12501224). This variant is absent in population databases (PM2). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3, PM2.

**Met criteria codes**

|                               |                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PS3</b>                    | ✓                                                                                                                                                                   | BioPKU: 42% enzyme activity. The co-expression of p.[E178G];[Q232E] showed 55.0% enzyme activity. PMID: 26803807                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                               |                                                                                                                                                                     | A dual eukaryotic vector system with two distinct PAH proteins N-terminally fused to different epitope tags was used to investigate the co-expression of PAH alleles reported in patients with inconsistent phenotypes. PAH variant proteins were transiently co-transfected in COS-7 cells. PAH activity was measured by liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS-MS), and protein expression was measured by Western blot. The co-expression of p.[E178G];[Q232E] showed 55.0% enzyme activity. <a href="#">PubMed:26803807</a> |
| <b>PM2</b>                    | ✓                                                                                                                                                                   | Absent from ExAC, gnomAD, 1000G, ESP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Not Met criteria codes</b> |                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>PP3</b>                    |   | Conflicting predictions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|                                                                                                    |  |  |
|----------------------------------------------------------------------------------------------------|--|--|
| Curation History  |  |  |
| <div><div></div><div>▼</div><div>▼</div></div>                                                     |  |  |
| Showing 1 to 1 of 1 rows                                                                           |  |  |
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