

Variant: *NM_000551.4(VHL):c.500G>A (p.Arg167Gln)*

Version: 1.0

CA020454 [↗](#)

2216 (ClinVar) [↗](#)

Gene: VHL ([HGNC:7428](#))

Condition: von Hippel-Lindau disease ([MONDO:0008667](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 4ea45f90-dbaf-4727-8a3b-44b9825cce21

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HGVS expressions

NM_000551.4(VHL):c.500G>A (p.Arg167Gln)

NM_000551.4:c.500G>A

NC_000003.12:g.10149823G>A

CM000665.2:g.10149823G>A

NC_000003.11:g.10191507G>A

CM000665.1:g.10191507G>A

NC_000003.10:g.10166507G>A

NG_008212.3:g.13189G>A

ENST00000696142.1:c.*177G>A

ENST00000696143.1:c.636G>A

ENST00000696153.1:c.611G>A

ENST00000256474.3:c.500G>A

ENST00000256474.2:c.500G>A

ENST00000345392.2:c.377G>A

ENST00000477538.1:n.636G>A

NM_000551.3:c.500G>A

NM_198156.2:c.377G>A

NM_001354723.1:c.*54G>A

NM_001354723.2:c.*54G>A

NM_198156.3:c.377G>A

Pathogenic

Met criteria codes 6

PM2_Supporting

PP3

PS3_Supporting

PM1

PS4

PM6

Not Met criteria codes 12

BA1

BP4

BP3

BP2

BP5

BP7

BS2

BS1

BS3

PVS1

PM5

PM4

Evidence Links 2

Expert Panel

VHL VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen VHL Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines for VHL Version 1.0.0

[↗](#) **Criteria Specification Approval History**

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

VHL VCEP

The NM_000551.4(VHL):c.500G>A (p.Arg167Gln) variant in VHL is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 167. This missense mutation has been identified in at least 19 unrelated individuals with von Hippel-Lindau disease. Mostly VHL Type 2 or 2B phenotypes are noted. However, some publications describe VHL Type 1 as well. PMIDs used: 20846682, 8707293, 9829912, 9829911, 7728151, 12114495, 12624160, 14722919. CIViC EIDs used (<https://civicdb.org>): 5485, 5354, 5264, 5062, 4913, 5487, 5546, 6118. 2 participating commercial laboratories reported >7 and >20 cases. The number of proband and/or family cases fulfills the criteria for strong evidence (PS4). Multiple publications (PMID: 15574766, PMID: 19030229) support disruption of Elongin C binding with the Arg167Gln variant, as well as altered regulation of HIF2a and near wild type regulation via ubiquitination of HIF1a (PS3_Supporting). A de novo (and mosaic ~5.5% allele freq in blood and ~34% in a pheochromocytoma at ~80% tumor purity) case was identified in a 16yo with no family history of VHL and fulfilling Danish Criteria for VHL (The 16yo had the following: Hb, pheochromocytoma, pancreatic endocrine tumor, left adrenal nodule). PMID: 30731206, CIViC evidence ID: EID7714. 1 commercial laboratory reports a de novo case in a child with bilateral retinal hemangiomas in the age range of 10yo (PM6). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Arg167 is one of the germline hotspots outlined by the VHL VCEP, and it is in the Elongin binding domain (PM1). The computational predictor REVEL gives a score of 0.874, which is above the threshold of >=0.664, evidence that correlates with impact to VHL function (PP3). Per VHL VCEP specifications, this code is applied when the REVEL score is >=0.6. (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal-dominant von Hippel-Lindau disease (VHL disease) based on the ACMG/AMP criteria applied, as specified by the ClinGen VHL VCEP Version 1.0 (Specifications approval date: 02/26/2024. Variant Approval Date 06/25/2024).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3			The computational predictor REVEL gives a score of 0.874, which is above the threshold of >0.664, evidence that correlates with impact to VHL function (PP3).
PS3_Supporting			Multiple publications support disruption of Elongin C binding with the Arg167Gln variant, as well as altered regulation of HIF2a and near wild type regulation via ubiquitination of HIF1a. Hacker et al shows R167Q confers partial suppression of HIF2a , inability to bind Elongin C and retains the ability to ubiquitinate HIF1a, similar to WT VHL. PubMed:19030229  Rathmell et al results display R167Q has impaired regulation of HIF2a, normal regulation of HIF1a, and impaired binding to Elongin C. PubMed:15574766 
PM1			Arg167 is one of the germline hotspots outlined by the VHL VCEP.
PS4			This missense mutation has been identified in >=19 unrelated individuals with Von Hippel Lindau disease. Mostly VHL Type 2 or 2B is noted, however, some describe VHL Type 1 as well. PMIDs used: 20846682, 8707293, 9829912, 9829911, 7728151, 12114495, 12624160, 14722919. CIViC EIDs used: 5485, 5354, 5264, 5062, 4913, 5487, 5546, 6118. 2 participating commercial laboratories reported >7 and >20 cases. The number of proband and/or family cases fulfills the criteria for strong evidence (PS4).
PM6			A de novo (and mosaic ~5.5% allele freq in blood and ~34% in a pheochromocytoma at ~80% tumor purity) case was identified in a 16yo with no family history of VHL and fulfilling Danish Criteria for VHL (The 16yo had the following: Hb, pheochromocytoma, pancreatic endocrine tumor, left adrenal nodule). PMID: 30731206, CIViC evidence ID: EID7714. 1 commercial laboratory reports a de novo case in a child with bilateral retinal hemangiomas in the age range of 10yo.

Not Met criteria codes			
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	The Arg167Trp variant is interpreted as pathogenic according to several groups, but has not been interpreted by the VHL VCEP specifications, therefor this code is not met.
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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