

Variant: NM_000551.4(VHL):c.191G>C (p.Arg64Pro)

Version: 1.0

CA020089 [↗](#)

2226 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 7122665e-2b75-4e58-a96a-965f11cf866f

Approved on: 2024/6/25

Published on: 2024/7/17

HGVS expressions

NM_000551.4(VHL):c.191G>C (p.Arg64Pro)

NM_000551.4:c.191G>C

NC_000003.12:g.10142038G>C

CM000665.2:g.10142038G>C

NC_000003.11:g.10183722G>C

CM000665.1:g.10183722G>C

NC_000003.10:g.10158722G>C

NG_008212.3:g.5404G>C

ENST00000696142.1:c.191G>C

ENST00000696143.1:c.191G>C

ENST00000696153.1:c.191G>C

ENST00000256474.3:c.191G>C

ENST00000256474.2:c.191G>C

ENST00000345392.2:c.191G>C

NM_000551.3:c.191G>C

NM_198156.2:c.191G>C

NM_001354723.1:c.191G>C

NM_001354723.2:c.191G>C

NM_198156.3:c.191G>C

Pathogenic

Met criteria codes 6

PM6_Supporting

PM2_Supporting

PS3_Supporting

PS4

PP3

PM1

Not Met criteria codes 1

PP1

Evidence Links 3

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**

Evidence submitted by expert panel

VHL VCEP

The NM_000551.3(VHL):c.191G>C (p.Arg64Pro) variant in the VHL gene is absent from gnomAD v4.1.0 (PM2_Supporting). This variant resides within a region, amino acids 63 - 155 (Beta domain), of VHL that is defined as a mutational hotspot and critical functional domain by the ClinGen VHL VCEP (PM1). The computational predictor REVEL gives a score of 0.938, which is above the threshold of 0.664, evidence that correlates with impact to VHL function (PP3). This variant has been reported in 11 probands with features of Von-Hippel-Lindau syndrome/ meeting Danish criteria (9.25 points, PS4; PMID: 19336503, 9663592, 17661816, 30455982, 28646318, 31383958, 19576851, 17639058, 28944243, 17102083, 21463266). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in an individual with bilateral pheochromocytoma (PM6_Supporting; PMID: 24555745). In vitro assays show conflicting results but suggest this variant impacts protein function as shown by reduced binding and ubiquitination of HIF-alpha (PMID: 16452184, 15611064, 11331612) (PS3_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal-dominant von Hippel Lindau syndrome (VHL syndrome) 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

PM6_Supporting	✓	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in an individual with bilateral pheochromocytoma (PM6_Supporting; PMID: 24555745).
PM2_Supporting	✓	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting	✓	In vitro assays show conflicting results but suggest this variant impacts protein function as shown by reduced binding and ubiquitination of HIF-alpha (PMID: 16452184, 15611064, 11331612) (PS3_Supporting). R64P retained ability to bind to ODD (oxygen-dependent degradation domain in HIF1a) but at reduced levels compared to WT pVHL (Figure 2A). Could polyubiquitinate HIF in vitro (Fig 2B). Could retain ability to bind to elongin B, C, and Cul2 (Fig 3). Figure 4: it downregulates HIF. Figure 6A: restored Fibronectin matrix deposition similar to WT. Note: no biological or technical replicates mentioned(?); positive and negative control present; no statistical analyses. PubMed:11331612 Table 1: R64P: HIFa binding is 50% of WT = reduced ability to bind HIFa (Fig 6B). Also cannot degrade HIF-2a (Fig 6D). But mutation preserves ability to form VEC complex (Fig 6A). PubMed:15611064 R64P failed to assemble fibronectin matrix (Fig 1A). Maintains ability to degrade HIF-2a (Fig 1B). Our variant has tumorigenic properties (Fig 2) and increased vascularization/ angiogenesis (Fig 3). Decreased expression of VEGF protein (Fig 4). All cells expressed significant levels of fibronectin and collagen IV regardless of their VHL status (Fig 5). Our variant is highly invasive (Fig 6: Matrigel Invasion assay). PubMed:16452184
PS4	✓	This variant has been reported in 11 probands with features of Von Hippel Lindau syndrome, or meeting Danish criteria (9.25 points, PS4; PMID: 19336503, 9663592, 17661816, 30455982, 28646318, 31383958, 19576851, 17639058, 28944243, 17102083, 21463266).
PP3	✓	The computational predictor REVEL gives a score of 0.938, which is above the threshold of 0.664, evidence that correlates with impact to VHL function (PP3).
PM1	✓	This variant resides within a region, amino acids 63 - 155 (B-domain), of VHL that is defined as a mutational hotspot and critical functional domain by the ClinGen VHL VCEP (PM1).

Not Met criteria codes

PP1

On Jan 11 call we determined the need to handle non-penetrance in cancer genes. We did not apply segregation data from the referenced paper.

Curation History [↗](#)

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