

Variant: *NM_000551.4(VHL):c.194C>G (p.Ser65Trp)*

Version: 1.0

CA020099 [↗](#)

43597 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: ae2d00be-c3ab-49cd-a347-b1fd19800735

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HGVS expressions

NM_000551.4:c.194C>G

NM_000551.4(VHL):c.194C>G (p.Ser65Trp)

NC_000003.12:g.10142041C>G

CM000665.2:g.10142041C>G

NC_000003.11:g.10183725C>G

CM000665.1:g.10183725C>G

NC_000003.10:g.10158725C>G

NG_008212.3:g.5407C>G

ENST00000696142.1:c.194C>G

ENST00000696143.1:c.194C>G

ENST00000696153.1:c.194C>G

ENST00000256474.3:c.194C>G

ENST00000256474.2:c.194C>G

ENST00000345392.2:c.194C>G

NM_000551.3:c.194C>G

NM_198156.2:c.194C>G

NM_001354723.1:c.194C>G

NM_001354723.2:c.194C>G

NM_198156.3:c.194C>G

Pathogenic

Met criteria codes 6

PS4

PP3

PM1

PM6

PM2_Supporting

PS3_Supporting

Not Met criteria codes 2

BA1

BS1

Evidence Links 0

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_000551.4(VHL):c.194C>G (p.Ser65Trp) variant in VHL is a missense variant predicted to cause substitution of Ser by Trp at amino acid 65 (p.Ser65Trp).The CIViC database (<https://civicdb.org>) describes 17 unrelated individuals with clinically diagnosed VHL or cancers in VHL cancer spectrum, many with evidence of VHL in family history. The following PMIDs were used for proband counting (2 unrelated probands or families where noted, all others 1) 28650583(2pt), 17024664, 17392848, 28388566(2pt), 29294023(2pt), 22156657, 23407287, 9829911, 7728151, 18446368, 22357542, 11148816, 21463266, 20518900. In addition, 3 participating laboratories contributed a total of 5 unique subjects. Each subject was evaluated for meeting Danish, Consistent or Nonspecific and a total of 13.5 points was awarded, which constitutes strong evidence. (PS4_Met). A denovo case, 33yo Chinese man presented with Renal Cell Carcinoma, and had a history of urological surgery at the age of 23 years due to an epididymal cyst and an ophthalmologic surgery at 26 years of age for retinal detachment resulting from bilateral retinal angiomas. 7 relatives (parents and siblings) were tested for S65W, and it was not identified. The authors do not note confirming maternity/paternity. PMID: 26622630 (PM6_Met). There is one variant present in gnomAD v4.1.0. The GroupMax Filtering Allele Frequency (95% CI) in gnomAD v4.1.0 is not calculated. PM2_Supporting can be applied for variants with <= 0.0000015 (0.00015%) frequency in gnomAD, or if no GroupMax Filtering Allele Frequency is calculated (due to a single variant present) (PM2_Supporting). S65W significantly decreases the VHL protein binding to HIF-1alpha, preventing ubiquitination PMID: 15611064 (PS3_Supporting). This variant resides within the VHL beta domain, a key functional domain. It is also defined as a mutational hotspot in Chinese populations (PMID:31620170) (PM1_Met). The computational predictor REVEL gives a score of 0.943, which is above the threshold of >0.664, evidence that correlates with impact to VHL function (PP3_Met). 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

PS4			The CIViC database (https://civicdb.org) describes 17 unrelated individuals with clinically diagnosed VHL or cancers in VHL cancer spectrum, many with evidence of VHL in family history. The following PMIDs were used for proband counting (2 unrelated probands or families where noted, all others 1) 28650583(2pt), 17024664, 17392848, 28388566(2pt), 29294023(2pt), 22156657, 23407287, 9829911, 7728151, 18446368, 22357542, 11148816, 21463266, 20518900. In addition, 3 participating laboratories contributed a total of 5 unique subjects. Each subject was evaluated for meeting Danish, Consistent or Nonspecific and a total of 13.5 points was awarded, which constitutes strong evidence. (PS4_Met).
PP3			The computational predictor REVEL gives a score of 0.943, which is above the threshold of >0.664, evidence that correlates with impact to VHL function (PP3_Met).
PM1			This variant resides within the VHL beta domain, a key functional domain. It is also defined as a mutational hotspot in Chinese populations (PMID:31620170) (PM1_Met).
PM6			A denovo case, 33yo Chinese man presented with Renal Cell Carcinoma, and had a history of urological surgery at the age of 23 years due to an epididymal cyst and an ophthalmologic surgery at 26 years of age for retinal detachment resulting from bilateral retinal angiomas. 7 relatives (parents and siblings) were tested for S65W, and it was not identified. The authors do not note confirming maternity/paternity. PMID: 26622630 (PM6_Met)
PM2_Supporting			There is one variant present in gnomAD v4.1.0. The GroupMax Filtering Allele Frequency (95% CI) in gnomAD v4.1.0 is not calculated. PM2_Supporting can be applied for variants with <= 0.0000015 (0.00015%) frequency in gnomAD, or if no GroupMax Filtering Allele Frequency is calculated (due to a single variant present) (PM2_Supporting).
PS3_Supporting			S65W significantly decreases the VHL protein binding to HIF-1alpha, preventing ubiquitination PMID: 15611064 (PS3_Supporting)

Not Met criteria codes

BA1			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

Curation History

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