

Variant: *NM_000551.4(VHL):c.264G>T (p.Trp88Cys)*

Version: 1.0

CA357078 [↗](#)

223171 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: c9e8934d-f33a-4a19-a9d0-85aaf41cebca

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HGVS expressions

NM_000551.4:c.264G>T

NM_000551.4(VHL):c.264G>T (p.Trp88Cys)

NC_000003.12:g.10142111G>T

CM000665.2:g.10142111G>T

NC_000003.11:g.10183795G>T

CM000665.1:g.10183795G>T

NC_000003.10:g.10158795G>T

NG_008212.3:g.5477G>T

ENST00000696142.1:c.264G>T

ENST00000696143.1:c.264G>T

ENST00000696153.1:c.264G>T

ENST00000256474.3:c.264G>T

ENST00000256474.2:c.264G>T

ENST00000345392.2:c.264G>T

NM_000551.3:c.264G>T

NM_198156.2:c.264G>T

NM_001354723.1:c.264G>T

NM_001354723.2:c.264G>T

NM_198156.3:c.264G>T

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PS3_Supporting

PS4_Moderate

PP3

PM1

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**

Evidence submitted by expert panel

VHL VCEP

The variant NM_000551.4(VHL):c.264G>T (p.Trp88Cys) is a missense variant predicted to cause substitution of Cysteine for Tryptophan at position 88. 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 (PM2_Supporting). Three commercial laboratories report at total of 6 cases harboring this variant, and sum to a total of 4 points (Moderate). Ambry: Case1 (0.5 points): 15-20yo with retinal hemangioblastomas; Case 2(0.5 points) 15-20yo with bilateral retinal hemangioblastomas; Gene DX: Case1(1 point) bilateral clear cell renal cell carcinoma and hemangioblastoma as a minor. Invitae: Case 1(0.5 points) Hemangioblastoma of thoracic spine and retinal angioma in 20s. Case 2 (1 point) Hemangioblastoma in CNS x2, pancreatic cysts, venal cyst in 30s. Case 3 (0.5 points) multiple bilateral enhancing cystic and solid renal masses and multiple pancreatic cystic lesions, highly suspicious for VHL in 30s. (PS4_Moderate). HIF degradation assays in mouse embryonic fibroblasts showed W88C was unable to degrade HIF1a or HIF2a compared to wild type VHL, indicting that this variant impacts protein functions (PMID:21715564) (PS3_Supporting). This variant is located in a mutational hotspot (PMID:35475554). There are multiple other nucleotide and amino acid substitutions at this position in ClinVar, including: NM_000551.4(VHL):c.264G>C (p.Trp88Cys), NM_000551.4(VHL):c.263G>C (p.Trp88Ser), NM_000551.4(VHL):c.262T>A (p.Trp88Arg), NM_000551.4(VHL):c.262T>C (p.Trp88Arg). (PM1). The computational predictor REVEL gives a score of 0.945, which is above the threshold of >=0.664, evidence that correlates with impact to VHL function (PP3). In summary, this variant meets the criteria to be classified as Likely 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

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			<div>HIF degradation assays in mouse embryonic fibroblasts showed W88C was unable to degrade HIF1a or HIF2a compared to wild type VHL, indicting that this variant impacts protein functions (PMID:21715564)(PS3_Supporting).</div> <div>HIF degradation assays in mouse embryonic fibroblasts showed W88C was unable to degrade HIF1a or HIF2a compared to wild type VHL, indicting that this variant impacts protein functions (PMID:21715564)(PS3_Supporting).</div> <div>PubMed:21715564 </div>
PS4_Moderate			Three commercial laboratories report at total of 6 cases harboring this variant, and sum to a total of 4 points (Moderate). Ambry: Case1 (0.5 points): 15-20yo with retinal hemangioblastomas; Case 2(0.5 points) 15-20yo with bilateral retinal hemangioblastomas; Gene DX: Case1(1 point) bilateral clear cell renal cell carcinoma and hemangioblastoma as a minor. Invitae: Case 1(0.5 points) Hemangioblastoma of thoracic spine and retinal angioma in 20s. Case 2 (1 point) Hemangioblastoma in CNS x2, pancreatic cysts, venal cyst in 30s. Case 3 (0.5 points) multiple bilateral enhancing cystic and solid renal masses and multiple pancreatic cystic lesions, highly suspicious for VHL in 30s. (PS4_Moderate).
PP3			The computational predictor REVEL gives a score of 0.945, which is above the threshold of >=0.664, evidence that correlates with impact to VHL function (PP3).
PM1			This variant is located in a mutational hotspot (PMID:35475554). There are multiple other nucleotide and amino acid substitutions at this position in ClinVar, including: NM_000551.4(VHL):c.264G>C (p.Trp88Cys), NM_000551.4(VHL):c.263G>C (p.Trp88Ser), NM_000551.4(VHL):c.262T>A (p.Trp88Arg), NM_000551.4(VHL):c.262T>C (p.Trp88Arg). (PM1)

Figure 4, hotspot analysis shows Trp88Cys is a germline hotspot in VHL. [PubMed:35475554](#) 

Curation History

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