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Variant: NM_000551.4(VHL):c.233A>G (p.Asn78Ser)

Version: 1.0

CA020131

93326 (ClinVar)

Gene: VHL (HGNC:7428)
Condition: von Hippel-Lindau disease (MONDO:0008667)
Inheritance Mode: Autosomal dominant inheritance
UUID: d9302a37-abf6-42b5-98a6-d489a1db8d27
Approved on: 2024/6/25
Published on: 2024/6/25

HGVS expressions

NM_000551.4:c.233A>G
NM_000551.4(VHL):c.233A>G (p.Asn78Ser)
NC_000003.12:g.10142080A>G
CM000665.2:g.10142080A>G
NC_000003.11:g.10183764A>G
CM000665.1:g.10183764A>G
NC_000003.10:g.10158764A>G
NG_008212.3:g.5446A>G
ENST00000696142.1:c.233A>G
ENST00000696143.1:c.233A>G
ENST00000696153.1:c.233A>G
ENST00000256474.3:c.233A>G
ENST00000256474.2:c.233A>G
ENST00000345392.2:c.233A>G
NM_000551.3:c.233A>G
NM_198156.2:c.233A>G
NM_001354723.1:c.233A>G
NM_001354723.2:c.233A>G
NM_198156.3:c.233A>G

Pathogenic

Met criteria codes 6

PM6 PM1 PS3_Supporting PS4 PM2_Supporting PP3

Evidence Links 1

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.233A>G (p.Asn78Ser) is a missense variant predicted to cause substitution of Asparagine by Serine. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This is identified in over 16 probands meeting either Danish criteria for VHL, or harboring other consistent features with VHL. The total phenotype points is 15.25, which meets the VHL VCEP specification of PS4 (5-15 phenotype points) (PMIDs:728151; 23842656; 25952756; 21463266; 25078357; 8634692; 23407287; 8707293; 8730290; 18067796; 12114495; 12202531; 17024664; 28388566; 18446368; 10567493; 29294023; 11850829) This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with VHL (PMID:12114495) (PM6). This variant is also seen 4 times in cancerhotspots.org, which meets the criteria of PM1_Supporting, when using somatic data to inform a germline variant curation. However, as the variant resides in the first Beta domain of VHL, a critical functional domain, it meets the full moderate criteria of (PM1). Functional data shows this variant did not alter expression of HIF1a (102% for HIF1α , similar to the truncating control used) and 86% expression for HIF2α (PS3_Supporting; PMID:21715564). The computational predictor REVEL gives a score of 0.767, 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 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	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with VHL (PMID:12114495) (PM6).
PM1	✔	This variant resides in the first Beta domain of VHL, a critical functional region. This variant is also seen 4 times in cancerhotspots.org, which meets the criteria of PM1_Supporting, when using somatic data to inform a germline variant curation. However, as the variant resides in the first Beta domain of VHL, it meets the full moderate criteria of (PM1).
PS3_Supporting	✔	This variant did not alter expression of HIF1a (102% for HIF1α , similar to the truncating control used) and 86% expression for HIF2α (PS3_Supporting). This variant did not alter expression of HIF1a (102% for HIF1α , similar to the truncating control used) and 86% expression for HIF2α. PubMed:21715564
PS4	✔	The variant has been reported in numerous unrelated probands and/or families meeting either VHL Type 1 or affected with VHL-related cancers (resulting in a VHL VCEP proband count of over 16, and VHL proband points of 15.25 - PS4). PMIDs: 7728151, 23842656, 25952756, 21463266, 11284029, 25078357, 8634692, 29294023, 23407287, 8707293, 8730290, 18067796, 12114495, 12202531, 17024664, 28388566, 18446368, 10567493. (PS4).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.767, which is above the threshold of >0.664, evidence that correlates with impact to VHL function (PP3).

Curation History

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