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# *Variant: NM_000552.5(VWF):c.4414G>C (p.Asp1472His)*

Version: 1.0

*CA6402534*

*256679 (ClinVar)*

**Gene**: VWF (HGNC:7450)
**Condition**: hereditary von Willebrand disease (MONDO:0019565)
**Inheritance Mode**: Undetermined mode of inheritance
**UUID:** 05530be7-7ee7-4644-8195-fd85d4a89fe4
**Approved on**: 2024-08-13
**Published on**: 2024-08-13

## *HGVS expressions*

**NM_000552.5:c.4414G>C**
NM_000552.5(VWF):c.4414G>C (p.Asp1472His)
NC_000012.12:g.6019004C>G
CM000674.2:g.6019004C>G
NC_000012.11:g.6128170C>G
CM000674.1:g.6128170C>G
NC_000012.10:g.5998431C>G
NG_009072.1:g.110667G>C
NG_009072.2:g.110667G>C
ENST00000261405.10:c.4414G>C
ENST00000261405.9:c.4414G>C
ENST00000538635.5:n.421-25070G>C
NM_000552.3:c.4414G>C
NM_000552.4:c.4414G>C

**Benign**

**Met criteria codes** 2

BP4 BA1

**Not Met criteria codes** 2

BS2 BP2

Evidence Links 0

Expert Panel

von Willebrand Disease VCEP

Criteria Specification Information

**Criteria Specification:** *ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0*
**Criteria Specification Approval History**
**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***von Willebrand Disease VCEP***

**The missense variant NM_000552.5(VWF):c.4414G>C (p.Asp1472His) is common in the general population with Grpmax filtering allele frequency of 0.5033 in gnomAD v4.1 (based on 38011/74882 alleles in the African/African American population). This is above the threshold of >0.1 (BA1). The computational predictor REVEL gives a score of 0.188, which is below the ClinGen VWD VCEP threshold of <0.290 and does not predict a damaging effect on VWF function (BP4). Additionally, the computational splicing predictor SpliceAI does not**

**predict an impact to splicing with this variant. This variant does appear to impact laboratory values; the mean VWF:RCo/VWF:Ag ratio of 0.75-0.82 was significantly reduced compared to 0.91-0.97 for WT in 275 healthy adult individuals harboring the Asp1472His variant (PMID:20231421). In summary this variant meets criteria to be classified as benign for von Willebrand disease based on the ACMG/AMP criteria applied, as specified by the ClinGen VWD: BA1, BP4.**

**Met criteria codes**

| | | |
|---|---|---|
| **BP4** | ✔ | The computational predictor REVEL gives a score of 0.188, which is below the ClinGen VWD VCEP threshold of <0.290 and does not predict a damaging effect on VWF function (BP4). Additionally, the computational splicing predictor SpliceAI indicated that the variant has no impact on splicing. |
| **BA1** | ✔ | This variant is common in the general population with a Grpmax filtering allele frequency in gnomAD v4.1 of 0.5033 (based on 38011/74882 alleles in the African/African American population). This is above the ClinGen VWD VCEP threshold of >0.1 (BA1). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **BS2** | ✖ | In PMID: 20231421 at least 275 healthy adult individuals harboring the D1472H variant were found to be unaffected with normal lab values, including normal bleeding scores, VWF:RCo/VWF:Ag ratios >0.6, and no increased response to low-dose ristocetin. Control individuals harboring the D1472H variant (268 heterozygotes and 13 homozygotes) had no diagnosis of a bleeding disorder (exclusion criteria included a previous diagnosis of VWD and known pregnancy). Only controls with completed bleeding scores (all <4), laboratory testing (including VWF:Ag ranging from 121-135 IU/dL, VWF:RCo ranging from 93-98 IU/dL, and RIPA which was not enhanced at low doses), and gene sequencing results are included. The mean VWF:RCo/VWF:Ag ratio of 0.75-0.82 was significantly reduced compared to 0.91-0.97 for WT, but above the threshold of <0.6. 6 of 281 control subjects with D1472H did have a VWF:RCo/VWF:Ag ratio less than 0.6 but none had elevated bleeding scores. In summary at least 275 healthy adult individuals harboring this variant were found to be unaffected with normal lab values (PMID: 20231421). BS2 is not considered due to incomplete penetrance. |
| **BP2** | ✖ | PMID: 22473027 patient 039 (with VWF:RCo/VWF:Ag ratio of 0.23) harbors both the Asp1472His variant and the Arg1308Cys variant (ClinVar 289, classified Pathogenic by the ClinGen VWD VCEP). PMID: 23520336 reported on 36 type 1 VWD subjects harboring Asp1472His, of which 81% had additional sequence variations, including not yet evaluated vWF variants Tyr1584Cys (ClinVar 310, VUS/Likely Pathogenic) and c.3108+5G>A (ClinVar 100246, VUS). The variants were not shown to be in cis with Asp1472His and if in trans are associated with type 1 VWD, which is not fully penetrant, so BP2 has not been applied. |

Curation History

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| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | NM_000552.5(VWF):c.4414G>C (p.Asp... | Benign | Hereditary Von Willebrand Disease | 2024-08-13 | 1.0 | ClinGen von Willebrand Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for VWF Version 1.0.0 | VWF |

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