Warfarin Sensitivity (CYP2C9, CYP2C cluster, CYP4F2, VKORC1) Genotyping

Content Review: July 2019 Last Update: December 2023

Warfarin (Coumadin) is an anticoagulant widely used throughout the world. Testing may be indicated for warfarin-naïve individuals prior to starting warfarin therapy, individuals with a personal or family history of difficulty with warfarin, and adherent patients taking warfarin but who are difficult to treat. Testing is also indicated for individuals currently on warfarin and required to discontinue therapy, such as prior to an invasive procedure or surgery, to estimate the time required to eliminate the drug. This test does not target variants associated with warfarin resistance.

Featured ARUP Testing

Warfarin Sensitivity (CYP2C9, CYP2C cluster, CYP4F2, VKORC1) Genotyping 3001541

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

Use to identify individuals with inherited variants that affect metabolism of (*CYP2C9* and *CYP2C* cluster) and/or sensitivity to (*CYP4F2*, *VKORC1*) warfarin

Refer to the Variants Tested table for more information.

Disease Overview

Pathophysiology

- Warfarin is administered as a racemic mixture; s-warfarin is more potent than r-warfarin and is thought to mediate most of the anticoagulant activity of warfarin.
- Primary mechanism of action is to inhibit vitamin K epoxide reductase (VKOR)
  - VKOR recycles vitamin K and activates clotting factors II, VII, IX, and X
- Exerts anticoagulant effects by reducing the concentration of these activated clotting factors

Diagnostic Issues

- Individual response to warfarin varies:
  - Factors affecting response include age, gender, body mass, diet, concomitant medications, and genetic variants.
  - An estimated 40-63% of the variability in therapeutic warfarin dose is accounted for by the *CYP2C9**2 and *3 and the *VKORC1**2 variant alleles.
  - The *CYP2C* cluster variant, rs12777823, common in people of African descent, with a minor allele frequency of approximately 25%, is found to be associated with a decreased warfarin dose requirement in this population.
- Overdosing and underdosing can result in life-threatening events (eg, bleeding or thrombosis).
  - Approximately 1% of individuals die due to bleeding complications associated with warfarin.
  - Approximately 15% of individuals experience minor bleeding complications.
- Dose adjustments are often necessary
  - Usually based on international normalized ratio (INR)
  - May be difficult to achieve therapeutic INR in some individuals (eg, those requiring <21 mg per week or >49 mg per week to maintain INR).

Genetics

Genes Tested

CYP2C9, CYP2C rs12777823, *CYP4F2, VKORC1*

Inheritance

Autosomal codominant

Variants Tested

Variants or groups of variants are classified as “star” (*) alleles for some genes such as *CYP2C9*, and functional phenotype is predicted based on international consensus nomenclature. However, not all variants on a chromosome/allele are interrogated and assumptions about phase are made, as shown below. More details about nomenclature, allele frequencies, and phenotype predictions are available at www.pharmvar.org or www.pharmgkb.org.

Gene (Transcript)	Alleles	Predicted Allele Function
CYP2C cluster (NC_000010)	*CYP2C*: rs12777823, g.96405502 G>A	Unclassified[a]
CYP2C9 (NM_000771)	*CYP2C9*2*: rs1799853, c.430C>T	Decreased function
	*CYP2C9*3*: rs1057910, c.1075A>C	Decreased function
	*CYP2C9*4*: rs56165452, c.1076T>C	Decreased function
	*CYP2C9*5*: rs28371686, c.1080C>G	Decreased function
	*CYP2C9*6*: rs9332131, c.818del	No function
	*CYP2C9*8*: rs7900194, c.449G>A	Decreased function
	*CYP2C9*11*: rs28371685, c.1003C>T	Decreased function
	*CYP2C9*12*: rs9332239, c.1465C>T	Decreased function
CYP4F2 (NM_001082)	*CYP4F2*3*: rs2108622, c.1297G>A (c.1275G>A [b])	Unclassified[c]
VKORC1 (NM_024006)	*VKORC1*2*: rs9923231, c.-1639G>A	Warfarin sensitivity

[a]The *CYP2C* cluster variant is associated with a decreased warfarin dose requirement in some people of African descent.

[b]PharmVar annotation.

[c]The *CYP4F2* variant is associated with increased warfarin dose requirements, particularly during initiation.

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: genetic factors and known non-genetic factors account for approximately 50% of the variability in warfarin dose[1]
- Analytic sensitivity and specificity: >99%

Results

- Variant(s) detected:
  - *VKORC1*2* allele is associated with reduced expression of the warfarin target, vitamin K epoxide reductase (VKOR), and a reduced dose requirement
  - The *CYP4F2*3* allele is associated with an increased dose requirement
  - *CYP2C9* variants are associated with a reduced rate of warfarin catabolism, which is associated with a decreased dose requirement and an increased time required to achieve steady state
    - Loading doses may be required
    - Vulnerability to drug-drug interactions may also be increased
  - The *CYP2C* cluster variant (rs12777823) is associated with a decreased dose requirement in some people of African descent, but is not included in algorithms intended for other populations. The mechanism underlying the association is not well characterized, but this variant was included in Tier 2 variant recommendations from the Association of Molecular Pathology and the College of American Pathologists.
- No variants detected: predictive of *1 functional allele
- Genotype should be interpreted with clinical information.
- Functional variants without clinical indication or impact on clinical management may not be reported.
- Genetic information and nongenetic factors can be used in combination with warfarin dose calculators, such as through www.WarfarinDosing.org.
- Additional dosing guidance is available through drug labeling and professional guidance documents, such as those published by the American College of Chest Physicians (CHEST) and the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Limitations

- Only the targeted genetic variants will be detected by this panel, and assumptions about phase and content are made to assign alleles.
- Diagnostic errors can occur due to rare sequence variations.
- Risk of therapeutic failure or adverse reactions with CYP2C9 substrates may be affected by genetic and nongenetic factors that are not detected by this test.
- This result does not replace the need for therapeutic drug or clinical monitoring.

References

1. Clinical Pharmacogenetics Implementation Consortium. CPIC guideline for pharmacogenetics-guided warfarin dosing. [Last modified: Apr 2019; Accessed: Apr 2019]

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