

PharmGKB Submission Update: VIII. PBAT Submission of Genetic Variation in *VKORC1* to the PharmGKB Network

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Category: genotype

Project: Pharmacogenetics, Biomarkers, and Anti-thrombotic Therapy

Table 1 provides the HUGO Gene Nomenclature Committee (HGNC) symbol, PharmGKB submission URL, submission date, and release date. Table 2 provides the HGNC symbol, HGNC name, synonym, GenBank accession numbers, and locus ID.

Pharmacogenetic Significance: *VKORC1* haplotype groups, defined by genotype at a novel loci in the region upstream of the transcription start site of the gene, can be used to stratify patients into low-, intermediate-, and high-dose warfarin groups and explain 21 to 25% of the variability in the therapeutic warfarin dose.

Pharmacological Significance: Warfarin is an effective anticoagulant that acts by antagonism of vitamin K to prevent γ -carboxylation of blood-clotting proteins (factors II, VII, IX, and X). The therapeutic index for warfarin is narrow, and polymorphisms in genes associated with warfarin pharmacokinetics (*CYP2C9*) and pharmacodynamics (*VKORC1*) influence clinical response, including risk of adverse events (including hemorrhage).

Article, publication date, and citation information can be found at <http://pharmrev.aspetjournals.org>.
doi:10.1124/pr.58.2.2.

Potential Drug Interactions: Amiodarone, cimetidine, metronidazole, omeprazole, zafirlukast, nandrolone, oxandrolone, oxymetholone, stanozolol, androgens, antifungals,azole, antithyroid agents, aspirin or other salicylates, cephalosporins, cinchophen, clofibrate, danazol, dextrothyroxine, diflunisal, disulfiram, fluvoxamine, lepirudin, paroxetine, propafenone, quinidine, sertraline, sulfapyridine, sulfasalazine, thyroid hormones, ticlopidine, zileuton, carbenicillin by injection, dipyridamole, divalproex, moxalactam, pentoxifylline, plicamycin, sulfinpyrazone, thrombolytic agents, ticarcillin, valproic acid, alcohol, barbiturates, carbamazepine, corticosteroids, glutethimide, griseofulvin, phenylbutazone, phenytoin, primidone, rifampin, vitamin K, simvastatin, and fluvastatin.

Functional Characteristics: The product of the *VKORC1* gene encodes the enzyme that reduces vitamin K 2,3-epoxide to the enzymatically activated form that is essential for γ -carboxylation of several blood-clotting proteins (factors II, VII, IX, and X). *VKORC1* haplotypes help explain differences in warfarin dose requirements. The molecular mechanism of this warfarin dose response seems to be regulated at the transcriptional level.

Summary of Data Submitted:

Size of sample set assayed: 340 (680 chromosomes)

Number of gene regions assayed: 4

Total bases assayed: 4

Coding bases: 0

Noncoding bases: 4

Number of variant sites: 4

Polymerase chain reaction primers reported: 8

TABLE 1
HGNC symbol, PharmGKB submission URL, submission date, and release date

HGNC Symbol	PharmGKB Submission	Submission Date	Release Date
<i>VKORC1</i>	http://www.pharmgkb.org/views/index.jsp?objId=PS204853&objCls=Submission	5/17/05	6/1/05

TABLE 2
HGNC symbol, HGNC name, synonym, GenBank accession numbers, and locus ID

HGNC Symbol	HGNC Name	Synonyms	GenBank Accession Nos.	Locus ID
<i>VKORC1</i>	Vitamin K epoxide reductase complex, subunit 1	<i>VKCFD2</i> , <i>VKOR</i> , IMAGE 3455200	AF176924, AK125618, AK129513, AK131087, AY358456, AY423044, AY466113, AY521634, AY587020, BC000828, BC002911, BI822140, CD249837	79001