Published in final edited form as:

Pharmacogenet Genomics. 2010 October ; 20(10): 642–644. doi:10.1097/FPC.0b013e32833433b6.

VKORC1 Pharmacogenomics Summary

Ryan P. Owen^a, Li Gong^a, Hersh Sagreiya^a, Teri E. Klein^a, and Russ B. Altman^{a,b}

^aDepartment of Genetics, Stanford University, Stanford, California, USA

^bDepartment of Bioengineering, Stanford University, Stanford, California, USA

Keywords

Vitamin K epoxide reductase; VKORC1; warfarin; pharmacogenetics; pharmacogenomics

The *VKORC1* gene encodes the VKORC1 (vitamin K epoxide reductase) protein, which is a key enzyme in the vitamin K cycle [1,2]. VKORC1 is a 163 amino acid integral membrane protein associated with the endoplasmic reticulum and VKORC1 mRNA is broadly expressed in many different tissues [3]. VKORC1 is responsible for the conversion of vitamin K epoxide to vitamin K, which is the rate-limiting step in the physiological process of vitamin K recycling [4]. The availability of reduced vitamin K is of particular importance for several coagulation factor proteins that require it as a cofactor, including factor VII, factor IX, and factor X [5]. VKORC1 is of therapeutic interest both for its role in contributing to high interpatient variability in coumarin anticoagulant dose requirements and as a potential player in vitamin K deficiency disorders [1].

Warfarin is a commonly prescribed oral anticoagulant used to prevent thromboembolic diseases in patients with deep vein thrombosis, atrial fibrillation, recurrent stroke or heart valve prosthesis [6]. Warfarin, as do other coumarin-type drugs with similar mechanisms of action, acts as an inhibitor of *VKORC1*; this leads to a reduced amount of vitamin K available to serve as a cofactor for clotting proteins [1]. Although effective warfarin dosing is challenging because of its narrow therapeutic index and high degree of interindividual variability in optimal dosing (between 0.6 and 15.5 mg/day) [7–10]. Inappropriate dosing of warfarin has been associated with a substantial risk of both major and minor hemorrhage [6,10,11]. As the pharmacological target of warfarin, *VKORC1* is considered a candidate gene for the variability in warfarin response.

Many studies that have attempted to explain the factors that influence warfarin response [6,12,13]. Before the cloning and characterization of *VKORC1*, it was known that the *CYP2C9* genotype of patients played a role in warfarin metabolism and response. The *CYP2C9* genotype of the patient explained approximately 10% of the observed variability in the therapeutic warfarin dose [14]. In 2004, *VKORC1* was cloned by two different groups, and some variants that conferred warfarin resistance were described [1,2]. The subsequent examination of other *VKORC1* variants has shown that polymorphisms in the *VKORC1* gene were associated with both high and low-warfarin dose phenotypes in humans. Overall, *VKORC1* polymorphisms account for approximately 25% of the variance in stabilized warfarin dose and many studies have consistently showed that *VKORC1* genotype seems to be the single biggest predictor of warfarin dose [13,15–17]. Other, nongenetic factors

including age, body mass index, sex, weight, and international normalized ratio are also known to play a role in warfarin response and collectively contribute to approximately 20% of variance in dose [18]. Some studies have attempted to define a warfarin dosing algorithm that takes into account both genetic and non-genetic factors predict an optimal warfarin dose [18,19]. In 2007, pharmacogenomic information for warfarin was approved by Food and Drug Administration to be included in the product label stating that *VKORC1* and *CYP2C9* genotypes may be useful in determining the optimal initial dose of warfarin [20]. A number of large-scale randomized clinical trials are now in progress to develop a globally applicable dosing strategy for warfarin.

***VKORC1* variants**

Several studies in independent populations have shown the importance of genetic variation in *VKORC1*, and a few important polymorphisms and haplotypes have been defined [9,21,22]. In the sections that follow, we summarize the importance of three of the most common and well-studied *VKORC1* polymorphisms. However, there have been several studies that we do not review [23–25] that examined the influence of rare *VKORC1* variants or variants that are more common in special populations.

Important variants (for full mapping information, see <http://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp>)

1. *VKORC1*: G3673A (rs9923231)
2. *VKORC1*: C6484T (rs9934438)
3. *VKORC1*: G9041A (rs7294)

G3673A (rs9923231)

G3673A, or – 1639 G > A as it is commonly called in the literature, is a polymorphism in the promoter region of *VKORC1* that is believed to be the causative single nucleotide polymorphism (SNP) for the low-dose phenotype. This polymorphism alters a *VKORC1* transcription factor binding site and luciferase assays show that the activity of the G allele is increased by 44% over the activity of the A allele [26]. In addition, analysis of *VKORC1* mRNA isolated from human liver samples showed that carriers of the A allele at position 3673 have reduced amounts of *VKORC1* mRNA [9]. The changes in gene expression presumably lead to fewer functional copies of the mature *VKORC1* protein, which is the rate-limiting enzyme in the vitamin K cycle. The G3673A or – 1639 G > A variant has been genotyped in a number of different populations (<https://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp>). This polymorphism has pronounced differences in its frequency by ethnic group; it is actually the majority allele (around 90%) in Asian populations and seems to explain the lower warfarin dose requirement for individuals of Asian descent. This variant is also quite common in Caucasians, with an allele frequency typically around 40% in predominantly Caucasian populations. The universal finding with this variant is that carriers of the A allele respond to a lower initial dose of warfarin than do carriers of the G allele (see above references). It should be noted that this effect is also additive, and that heterozygotes respond to an intermediate warfarin dose, and homozygous carriers of the A allele respond to the lowest dose of warfarin and are at the highest risk for warfarin-related adverse events [9]. Recent clinical studies showed that individuals with the A allele require a 28% decrease in the therapeutic warfarin dose per allele and this SNP is the most important predictor of initiation dose for warfarin [19].

C6484T (rs9934438)

C6484T, or 1173C > T, is a SNP in the first intron of *VKORC1*. It is in near perfect linkage disequilibrium with G3673A. C6484T was the first SNP associated with the low-dose warfarin phenotype [23], and although it is believed to be functionally inert, C6484T is still very commonly used as a marker SNP for G3673A and for haplotypes containing this variant (<https://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp> for an allele frequency table). Comparison of this table with that of the frequencies in G3673A shows similar allele frequencies. Some of the studies genotyped both SNPs with similar, if not identical, frequency results.

G9041A (rs7294)

G9041A, or 3730 G > A, is a SNP in the 3'UTR of *VKORC1*, and it may be associated with a higher warfarin dose [23,27]. It is generally not found in the same haplotypes as G3673A or C6484T (<https://www.pharmgkb.org/search/annotatedGene/vkorc1/variant.jsp> for allele frequency table).

There are different attempts in the literature to define *VKORC1* haplotype structure. The systems agree that haplotypes containing the G3730A variant are reduced function haplotypes of *VKORC1*, but the nomenclature is varied. In the full *VKORC1* VIP report, an effort is made to distinguish between the existing types of haplotype nomenclature and to describe what effect each haplotype has on warfarin therapy (<https://www.pharmgkb.org/search/annotatedGene/vkorc1/haplotype.jsp>).

In summary, *VKORC1* polymorphisms can significantly alter warfarin pharmacodynamics and maintenance dose requirement. Patients with the 1639A (rs992323) and 1173T (rs9934438) allele require a lower warfarin dose (mean dose 24–26 mg/week) compared with 35 mg/week for the wild-type carriers [28]. Patients with 9041A (rs7294) need a higher warfarin dose (mean dose 40 mg/week) [27,28]. Incorporating *VKORC1* and *CYP2C9* genotype information and clinical factors such as age and weight into the warfarin dosing equation holds great promise to select the optimal dose for the individual patient at the start of warfarin therapy.

Acknowledgments

PharmGKB is supported by the NIH/NIGMS Pharmacogenetics Research Network and Database (UO1GM61374).

References

1. Rost S, Fregin A, Ivaskevicius V, Conzelmann E, Hortnagel K, Pelz HJ, et al. Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature*. 2004; 427:537–541. [PubMed: 14765194]
2. Li T, Chang CY, Jin DY, Lin PJ, Khvorova A, Stafford DW. Identification of the gene for vitamin K epoxide reductase. *Nature*. 2004; 427:541–544. [PubMed: 14765195]
3. Oldenburg J, Bevens CG, Muller CR, Watzka M. Vitamin K epoxide reductase complex subunit 1 (*VKORC1*): the key protein of the vitamin K cycle. *Antioxid Redox Signal*. 2006; 8:347–353. [PubMed: 16677080]
4. Wajih N, Sane DC, Hutson SM, Wallin R. Engineering of a recombinant vitamin K-dependent gamma-carboxylation system with enhanced gamma-carboxyglutamic acid forming capacity: evidence for a functional CXXC redox center in the system. *J Biol Chem*. 2005; 280:10540–10547. [PubMed: 15640149]
5. Stafford DW. The vitamin K cycle. *J Thromb Haemost*. 2005; 3:1873–1878. [PubMed: 16102054]
6. Rettie AE, Tai G. The pharmacogenomics of warfarin: closing in on personalized medicine. *Mol Interv*. 2006; 6:223–227. [PubMed: 16960144]

7. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, Srinouanprachanh SL, Farin FM, Rettie AE. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA*. 2002; 287:1690–1698. [PubMed: 11926893]
8. Takahashi H, Echizen H. Pharmacogenetics of CYP2C9 and interindividual variability in anticoagulant response to warfarin. *Pharmacogenomics J*. 2003; 3:202–214. [PubMed: 12931134]
9. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med*. 2005; 352:2285–2293. [PubMed: 15930419]
10. Kamali F. Genetic influences on the response to warfarin. *Curr Opin Hematol*. 2006; 13:357–361. [PubMed: 16888441]
11. Wadelius M, Pirmohamed M. Pharmacogenetics of warfarin: current status and future challenges. *Pharmacogenomics J*. 2007; 7:99–111. [PubMed: 16983400]
12. Kamali F, Pirmohamed M. The future prospects of pharmacogenetics in oral anticoagulation therapy. *Br J Clin Pharmacol*. 2006; 61:746–751. [PubMed: 16722840]
13. Yin T, Miyata T. Warfarin dose and the pharmacogenomics of CYP2C9 and VKORC1-rationale and perspectives. *Thromb Res*. 2007; 120:1–10. [PubMed: 17161452]
14. Wadelius M, Sorlin K, Wallerman O, Karlsson J, Yue QY, Magnusson PK, et al. Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. *Pharmacogenomics J*. 2004; 4:40–48. [PubMed: 14676821]
15. Wen MS, Lee M, Chen JJ, Chuang HP, Lu LS, Chen CH, et al. Prospective study of warfarin dosage requirements based on CYP2C9 and VKORC1 genotypes. *Clin Pharmacol Ther*. 2008; 84:83–89. [PubMed: 18183038]
16. Cooper GM, Johnson JA, Langaee TY, Feng H, Stanaway IB, Schwarz UI, et al. A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. *Blood*. 2008; 112:1022–1027. [PubMed: 18535201]
17. Wadelius M, Chen LY, Lindh JD, Eriksson N, Ghorri MJ, Bumpstead S, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood*. 2009; 113:784–792. [PubMed: 18574025]
18. Sconce EA, Kamali F. Appraisal of current vitamin K dosing algorithms for the reversal of over-anticoagulation with warfarin: the need for a more tailored dosing regimen. *Eur J Haematol*. 2006; 77:457–462. [PubMed: 17042764]
19. Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther*. 2008; 84:326–331. [PubMed: 18305455]
20. Gage BF, Lesko LJ. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. *J Thromb Thrombolysis*. 2008; 25:45–51. [PubMed: 17906972]
21. Geisen C, Watzka M, Sittinger K, Steffens M, Daugela L, Seifried E, et al. VKORC1 haplotypes and their impact on the inter-individual and inter-ethnic variability of oral anticoagulation. *Thromb Haemost*. 2005; 94:773–779. [PubMed: 16270629]
22. Rettie AE, Farin FM, Beri NG, Srinouanprachanh SL, Rieder MJ, Thijssen HH. A case study of acenocoumarol sensitivity and genotype-phenotype discordancy explained by combinations of polymorphisms in VKORC1 and CYP2C9. *Br J Clin Pharmacol*. 2006; 62:617–620. [PubMed: 16869821]
23. D'Andrea G, D'Ambrosio RL, Di Perna P, Chetta M, Santacroce R, Brancaccio V, et al. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood*. 2005; 105:645–649. [PubMed: 15358623]
24. D'Ambrosio RL, D'Andrea G, Cafolla A, Faillace F, Margaglione M. A new vitamin K epoxide reductase complex subunit-1 (VKORC1) mutation in a patient with decreased stability of CYP2C9 enzyme. *J Thromb Haemost*. 2007; 5:191–193. [PubMed: 17059426]
25. Loebstein R, Dvoskin I, Halkin H, Vecsler M, Lubetsky A, Rechavi G, et al. A coding VKORC1 Asp36Tyr polymorphism predisposes to warfarin resistance. *Blood*. 2007; 109:2477–2480. [PubMed: 17110455]

26. Yuan HY, Chen JJ, Lee MT, Wung JC, Chen YF, Charng MJ, et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Hum Mol Genet.* 2005; 14:1745–1751. [PubMed: 15888487]
27. Herman D, Peternel P, Stegnar M, Breskvar K, Dolzan V. The influence of sequence variations in factor VII, gamma-glutamyl carboxylase and vitamin K epoxide reductase complex genes on warfarin dose requirement. *Thromb Haemost.* 2006; 95:782–787. [PubMed: 16676068]
28. Wadelius M, Chen LY, Downes K, Ghorri J, Hunt S, Eriksson N, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenomics J.* 2005; 5:262–270. [PubMed: 15883587]