**Supplementary Table S1.** **Genes involved in warfarin’s mechanism of action.**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Pathway (Wadelius et al., 2007;Wadelius and Pirmohamed, 2007)** | **Gene (NCBI gene ID) (National Center for Biotechnology Information, 2018)** | **Protein function**  **(NCBI, (National Center for Biotechnology Information, 2018) unless otherwise)** | **Examples of SNPs (unless shown otherwise, examples are from (Wadelius et al., 2007))** | | | | |
| **Reference SNP ID (National Center for Biotechnology Information, 2018)** | **Location** | **Effects** | | **MAF (1000’s genome project) (European Bioinformatics lnstitute, 2018)** |
| **Functional** | **On warfarin dosing** |
| **Vitamin K Biotransformation** | | | | | | | |
| *Vitamin K cycle* | | | | | | | |
| Vitamin K epoxide reductase | *VKORC1* (79001) | A hepatic epoxide hydrolase that catalyses the reduction of vitamin K 2,3-epoxide. It is warfarin’s molecular target. | rs9923231  (*G3673A* or –*1639G>A*) | Promoter region (5' UTR) | Alters a *VKORC1* transcription factor binding site (E-Box, consensus sequence *CANNTG* that may function as a repressor binding site, in the 5’ UTR). An *A>G* mutation abolishes the E-box consensus increasing the promoter activity by 44% (Yuan et al., 2005). The reverse *G>A* mutation re-instates the consensus leading to reduced transcription/amounts of mRNA and fewer functional copies of the VKORC1 protein (Rieder et al., 2005;Yuan et al., 2005). This mechanism is yet to be confirmed. This SNP is in near perfect LD with others e.g. rs9934438 below (Daly, 2013). | The *A* allele is associated with a low-dose (reduced doses up to 3 mg/day) (Jorgensen et al., 2012). It is the most important predictor of warfarin dose explaining ~27% of the variance in warfarin maintenance dose in Caucasians and Asians (only ~9% of dose variability in African Americans is explained, attributable to a lower allele frequency) (Asiimwe et al., 2021). | AFR = 0.05  AMR = 0.41  EAS = 0.89  EUR = 0.39  SAS = 0.15 |
| rs9934438  (*C6484T* or *1173C>T*) | Intronic | Unknown function (D'Andrea et al., 2005). | First SNP to be associated with a low-dose warfarin phenotype (D'Andrea et al., 2005). | AFR = 0.05  AMR = 0.41  EAS = 0.89  EUR = 0.39  SAS = 0.15 |
| Epoxide hydrolase 1, microsomal | *EPHX1* (2052) | Biotransformation enzyme (Pautas et al., 2010;Ciccacci et al., 2011). | rs1051740 | Coding | Unknown function (Loebstein et al., 2005). | Likely to increase warfarin dose requirements (Loebstein et al., 2005;Schelleman et al., 2010). | AFR = 0.14  AMR = 0.32  EAS = 0.48  EUR = 0.30  SAS = 0.38 |
| NAD(P)H dehydrogenase,  quinone 1 | *NQO1* (1728) | A detoxifying enzyme that can reduce the vitamin K quinone (Wallin and Hutson, 1982;Ross and Siegel, 2004). | rs1437135 | Intronic | Associated with protein C levels (Buil et al., 2004). | Lower protein C levels increase thrombotic risk which may necessitate increased warfarin doses. | AFR = 0.26  AMR = 0.34  EAS = 0.42  EUR = 0.21  SAS = 0.36 |
| Calumenin | *CALU* (813) | Inhibits GGCX | rs339097 | Intronic | Associated with higher *CALU* expression although it remains unclear if affects mRNA expression or stability or is in LD with causative SNP(s) (Voora et al., 2010). | Associated with higher warfarin dose requirements in African Americans (Voora et al., 2010;Ramirez et al., 2012). | AFR = 0.14  AMR = 0.01  EAS = 0.01  EUR = 0.00  SAS = 0.01 |
| Gamma-glutamyl  carboxylase | *GGCX* (2677) | Carboxylates vitamin K dependent coagulation factors/proteins (Rost et al., 2004). | rs699664 | Coding | Unknown function (Loebstein et al., 2005). | Associated with higher dose in European and Asian patients (Wadelius et al., 2005;Kimura et al., 2007;Huang et al., 2011;Kamali et al., 2013) but not in African Americans (Schelleman et al., 2010;Cavallari et al., 2012;Ramirez et al., 2012). | AFR = 0.663  AMR = 0.269  EAS = 0.310  EUR = 0.367  SAS = 0.151 |

**Supplementary Table S1. Continued.**

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| **Pathway (Wadelius et al., 2007;Wadelius and Pirmohamed, 2007)** | **Gene (NCBI gene ID) (National Center for Biotechnology Information, 2018)** | **Protein function**  **(NCBI, (National Center for Biotechnology Information, 2018) unless otherwise)** | **Examples of SNPs (unless shown otherwise, examples are from (Wadelius et al., 2007))** | | | | |
| **Reference SNP ID (National Center for Biotechnology Information, 2018)** | **Location** | **Effects** | | **MAF (1000’s genome project) (European Bioinformatics lnstitute, 2018)** |
| **Functional** | **On warfarin dosing** |
| *Vitamin K metabolism* | | | | | | | |
| Cytochrome P450 4F2 | *CYP4F2* (8592) | A vitamin K oxidase that catalyzes the metabolism of vitamin K to hydroxyl-vitamin K1 (Caldwell et al., 2008). | rs2108622  (*1297G>A, CYP4F2\*3* or V433M) | Coding | Encodes a protein with decreased activity hence increased vitamin K levels and warfarin resistance (Caldwell et al., 2008;McDonald et al., 2009). | Higher warfarin dose requirements in Caucasians and Asians (Caldwell et al., 2008;Takeuchi et al., 2009;Cha et al., 2010;Liang et al., 2012;Johnson and Cavallari, 2015) but not in African Americans (Perera et al., 2013;Shendre et al., 2016). It however explains only an additional 1–2% of observed warfarin dose variability in Caucasians/Asians (Takeuchi et al., 2009;Cha et al., 2010). | AFR = 0.08  AMR = 0.24  EAS = 0.21  EUR = 0.29  SAS = 0.41 |
| *Vitamin K-dependent proteins (other genes not detailed include: F9 (gene ID 2158), F10 (2159), PROS1 (5627), and GAS6 (2621))* | | | | | | | |
| Coagulation factor II, prothrombin | *F2* (2147) | Converts fibrinogen to fibrin, activates FV, FVIII, FXIII and protein C (Berkner, 2000;Dahlback, 2005). | rs5896 | Coding | Function unknown. | May increase warfarin sensitivity (D'Ambrosio et al., 2004;Shikata et al., 2004). | AFR = 0.01  AMR = 0.28  EAS = 0.60  EUR = 0.12  SAS = 0.17 |
| Coagulation factor VII | *F7* (2155) | FVIIa converts FIX to FIXa and FX to FXa (Berkner, 2000;Dahlback, 2005). | rs6046 | Coding | Associated with reduced concentration and activity of the active protein (Arbini et al., 1994;Mlynarsky et al., 2012). | Associated with lower warfarin doses in Israelites (Mlynarsky et al., 2012). | AFR = 0.12  AMR = 0.12  EAS = 0.05  EUR = 0.11  SAS = 0.30 |
| Protein C | *PROC* (5624) | Activated protein C inactivates FVa and VIIIa (Berkner, 2000;Dahlback, 2005). | rs1799809 | Regulatory region | Lower protein C activity (Spek et al., 1995;Aiach et al., 1999). | Lower protein C levels increase thrombotic risk which may necessitate increased warfarin doses. | AFR = 0.26  AMR = 0.71  EAS = 0.82  EUR = 0.59  SAS = 0.62 |
| Protein Z | *PROZ* (8858) | Is a cofactor for the inactivation of FXa (Berkner, 2000;Broze, 2001). | rs3024711 | Intron | Function unknown. | Unclear effects. | AFR = 0.06  AMR = 0.22  EAS = 0.30  EUR = 0.17  SAS = 0.44 |
| *Other coagulation proteins (another gene example not detailed is SERPINC1, ID 462)* | | | | | | | |
| Coagulation factor V | *F5* (2153) | A cofactor that activates FII and FXa. | rs6025 | Coding | FV Leiden increased risk of thrombosis (Bertina et al., 1994;Dahlback, 2005). | Increased thrombotic risk implies increased warfarin dose requirements. | AFR = 0.00  AMR = 0.01  EAS = 0.00  EUR = 0.01  SAS = 0.01 |

**Supplementary Table S1. Continued.**

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| **Pathway (Wadelius et al., 2007;Wadelius and Pirmohamed, 2007)** | **Gene (NCBI gene ID) (National Center for Biotechnology Information, 2018)** | **Protein function**  **(NCBI, (National Center for Biotechnology Information, 2018) unless otherwise)** | **Examples of SNPs (unless shown otherwise, examples are from (Wadelius et al., 2007))** | | | | |
| **Reference SNP ID (National Center for Biotechnology Information, 2018)** | **Location** | **Effects** | | **MAF (1000’s genome project) (European Bioinformatics lnstitute, 2018)** |
| **Functional** | **On warfarin dosing** |
| *Transportation* | | | | | | | |
| Apolipoprotein E | *APOE* (348) | Serves as a ligand for vitamin K-uptake mediating receptors.(Berkner and Runge, 2004) | rs429358 | Coding | These 2 SNPs discriminate between the haplotypes ε2, ε3 and ε4 which are respectively associated with low, intermediate and high vitamin K uptake (Schelleman et al., 2007). | ε2ε2 genotype associated with lower warfarin doses than ε3ε3 or ε4ε4 (Yu et al., 2016). | AFR = 0.27  AMR = 0.10  EAS = 0.09  EUR = 0.16  SAS = 0.09 |
| rs7412 | Coding | AFR = 0.10  AMR = 0.05  EAS = 0.10  EUR = 0.06  SAS = 0.04 |
| ***Warfarin biotransformation*** | | | | | | | |
| *Metabolism (other genes not detailed include: CYP2C8 (ID 1558), CYP2C18 (1562), CYP2C19 (1557), CYP1A1 (1543), CYP1A2 (1544), CYP3A4 (1576), and CYP3A5 (1577)).* | | | | | | | |
| Cytochrome P450 2C9 | *CYP2C9* (1559) | Polymorphic hepatic drug metabolising enzyme (S-warfarin). | rs1799853 (*430C>T, R144C, \*2*) | Coding | About 12% of wild-type activity (Rettie et al., 1994;Haining et al., 1996;Crespi and Miller, 1997). | Leads to a reduction in warfarin dose by up to 1.5 mg/day (Jorgensen et al., 2012). | AFR = 0.01  AMR = 0.10  EAS = 0.00  EUR = 0.12  SAS = 0.04 |
| rs1057910 (*1075A>C, I359L \*3*) | Coding | <5% as efficient as the wild-type enzyme (Rettie et al., 1994;Haining et al., 1996;Sullivan-Klose et al., 1996;Crespi and Miller, 1997) . | Leads to reduction in dose by up to 2.6 mg/day (Jorgensen et al., 2012). | AFR = 0.00  AMR = 0.04  EAS = 0.03  EUR = 0.07  SAS = 0.11 |
| rs28371686 (*1080 C>G, D360E, \*5*) | Coding | Reduced and null (\*6) enzyme activity. | Leads to lower dose requirements, especially in populations of African ancestry (Asiimwe et al., 2020). Overall, *CYP2C9* genotype accounts for ~7–10% of warfarin dose variability (Johnson and Cavallari, 2013;Johnson et al., 2017). | AFR = 0.02  Others ~ 0.00 |
| rs9332131 (818delA, *\*6*) | Coding | AFR = 0.01  Others ~ 0.00 |
| rs7900194 (*449 G>A, R150H, \*8*) | Coding | AFR = 0.05  Others ~ 0.00 |
| rs28371685 (1003 A>G, R335W, \*11) | Coding | AFR = 0.02  Others ~ 0.00 |
| rs12777823 | (*CYP2C* gene cluster region) | Associated with alterations in warfarin clearance. May be in LD with another variant because the effect is observed only in African Americans (Perera et al., 2013). | Heterozygous or homozygous African Americans (A allele) respectively require a dose reduction of ~ 7 or 9 mg/week (Perera et al., 2013). | AFR = 0.251  AMR = 0.107  EAS = 0.314  EUR = 0.151  SAS = 0.362 |

**Supplementary Table S1. Continued.**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Pathway (Wadelius et al., 2007;Wadelius and Pirmohamed, 2007)** | **Gene (NCBI gene ID) (National Center for Biotechnology Information, 2018)** | **Protein function**  **(NCBI, (National Center for Biotechnology Information, 2018) unless otherwise)** | **Examples of SNPs (unless shown otherwise, examples are from (Wadelius et al., 2007))** | | | | |
| **Reference SNP ID (National Center for Biotechnology Information, 2018)** | **Location** | **Effects** | | **MAF (1000’s genome project) (European Bioinformatics lnstitute, 2018)** |
| **Functional** | **On warfarin dosing** |
| *Cytochrome P450 inducibility* | | | | | | | |
| Pregnane X receptor (PXR) | NR1I2 (8856) | Mediates induction of *CYP2C9*, other CYP enzymes and *ABCB1* (Chen et al., 2004). | rs2472682 | Intronic | Unknown function. | Variant homozygote carriers required significantly lower daily doses than wild-type homozygotes by about 0.8 mg. This SNP accounted for 2.3% of dose variability (Moon et al., 2015). | AFR = 0.15  AMR = 0.65  EAS = 0.38  EUR = 0.66  SAS = 0.55 |
| Constitutive androstane receptor (CAR) | NR1I3 (9970) | Transcriptional regulation of several genes e.g. *CYP2C9* (Assenat et al., 2004). | rs2501873 | Intronic | Unknown function. | Lower dosing. Accounted for 1.3% of variability in warfarin dose (Moon et al., 2015). | AFR = 0.31  AMR = 0.52  EAS = 0.43  EUR = 0.56  SAS = 0.52 |
| *Transportation (another gene not detailed is ORM2, ID 5005)* | | | | | | | |
| P-glycoprotein, Multidrg resistance protein 1 | *ABCB1* (5243) | A xenobiotics cellular efflux pump (Kroetz et al., 2003). | rs2032582 | Coding | Warfarin is a week inhibitor and maybe a substrate (Sussman et al., 2002). | Could theoretically increase dose requirements. | AFR = 0.00  AMR = 0.06  EAS = 0.13  EUR = 0.02  SAS = 0.05 |
| Alpha-1-acid glycolprotein 1, Oroso-cumoid 1 | *ORM1* (5004) | A warfarin carrier in plasma.(Nakagawa et al., 2003) | rs1687390 | Regulatory region | Unknown function. | Could decrease dose requirements. | AFR = 0.30  AMR = 0.07  EAS = 0.00 |

Abbreviations: *ABCB1*, P-glycoprotein gene or *MDR1* gene; AFR, African; AMR, American; *APOE*, Apolipoprotein E gene; *CALU*, Calumenin gene; *CAR*, Constitutive androstane receptor; *CYP*, Cytochrome P450; EAS, East Asian; *EPHX1*, Epoxide hydrolase 1, microsomal gene; EUR, European; *GAS6*, Growth-arrest specific 6; *GGCX*, Gamma-glutamyl carboxylase gene; *F2*, Coagulation factor II gene or prothrombin gene; *F5*, Coagulation factor V gene; *F7*, Coagulation factor VII gene; *F9*, Coagulation factor IX gene; *F10*, Coagulation factor X gene; *FII*, Coagulation factor II or prothrombin (additional a, if any, stands for activated); *FV*, Coagulation factor V; *FVII*, Coagulation factor VII; FIX, Coagulation factor IX; FX, Coagulation factor X; ID, identification; LD, linkage disequilibrium; *NQO1*, NAD(P)H dehydrogenase, quinone 1 gene; *MDR1*, Multidrug resistance protein 1; NCBI, U.S. National Center for Biotechnology Information; *NR1I2*, Pregnane X receptor gene; *NR1I3*, Constitutive androstane receptor gene; *ORM1*, Orosomucoid 1 gene or Alpha-1-acid glycoprotein 1 gene; *ORM2*, Orosomucoid 2 gene or Alpha-1-acid glycoprotein 2 gene; *PROC*, Protein C gene; *PROS1*, Protein S gene; *PROZ*, Protein Z gene; *PXR*, Pregnane X receptor; SAS, South Asian; *SERPINC1*, Anti-thrombin III gene; SNP, Single nucleotide polymorphism; UTR, Untranslated region; *VKOR*, vitamin K epoxide reductase complex.

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