VKORC1 polymorphisms and warfarin maintenance dose in population of Sakha (Yakuts)

Y.V. Chertovskikh*a, E.U. Malova*b,*, N.R. Maksimova*c, N.V. Popova*d and D.A. Sychev*e

*a Ministry of Health of the Republic of Sakha (Yakutiya), Yakutsk, Russia
*bI.M. Sechenov; First Moscow State Medical University, Moscow, Russia
*cLaboratory of Genomic Medicine, Yakutsk, Russia
*dCenter for Personalized Medicine, Yakutsk, Russia
*eRussian Medical Academy of Postgraduate Education, Moscow, Russia

*Corresponding author. E-mail: malovapmgmu@gmail.com

BACKGROUND: Vitamin K antagonists are effective in the prevention and treatment of thromboembolic disorders. Warfarin is one of the most widely prescribed vitamin K antagonists in the world [1, 2]. It has a narrow therapeutic range and a given dose may result in a large inter-individual variation of response. Insufficient dose may fail to prevent thromboembolism, while an overdose increases the risk of bleeding. Patient-specific factors (e.g., age, body size, race, concurrent diseases, and medications) explain some of the variability in warfarin dosage, but genetic factors influencing warfarin response explain a significantly higher proportion of this variability [3]. Molecular analysis of the gene that encodes the target enzyme vitamin K epoxide reductase complex 1 (VKORC1) strongly suggests that its genetic variations greatly affect the individual response to oral anticoagulants [4–7].

OBJECTIVE: To evaluate effects of VKORC1 polymorphisms on warfarin dose excess anticoagulation (INR >4.0) in the population of Sakha (S) patients.

METHODS: 53 patients (29-women, 24-men) with atrial fibrillation (68%), congestive heart failure (60%), hypertension (49%) and cardiac valve replacement (26%) were recruited. The age range was 26–80 years, with a mean age of 62.87 ± 12.57 years.

International normalized ratio and plasma warfarin concentrations were determined. Genotyping was carried out by RT-PCR (real-time PCR). The three genetic polymorphisms of the gene VKORC1 G3673A (rs9923231) were studied: normal (GG), heterozygous (GA) and homozygous (AA). Fisher exact probability test and chi-square test (with Yates correction) were applied to compare data among the AA and GG + GA groups; also Mann-Whitney test was used.

RESULTS: The median maintenance daily dose of warfarin among AA carriers was 3.0 mg/day [1.25–7.5 mg], while in GG and GA patients it was 3.13 mg/day [1.88–7.92 mg]. The mean daily warfarin dosage was higher in GG and GA genotype carriers 4.05 mg/day (SD±1.7) than in patients with AA genotype 3.13 (SD±1.5). Differences are of borderline significance (p = 0.054).
Of the 41 patients who required warfarin doses of less than 5 mg, 28 (63%) were found to be AA carriers and 14 (37%) were GG, GA carriers. Differences were not quite significant ($p = 0.072$). Among 31 homozygous polymorphism carriers 2 (4%) patients developed overanticoagulation (INR >4.0), while among 22 normal and heterozygous polymorphisms carriers only 3 (6%) patients developed overanticoagulation (INR >4.0). Differences were not statistically significant ($p = 0.36$).

**CONCLUSIONS:** No significant association between VKORC1 polymorphisms and the frequency of excess anticoagulation (INR >4.0) was found. This may be explained by the number of cases included. AA polymorphisms compared to other polymorphisms shows borderline difference in the warfarin dose. The results can be used for the development of a pharmacogenetic-guided warfarin dosing algorithm.

Keywords: Polymorphisms of the VKORC1 gene on maintenance warfarin dose in the population of sakha (yakuts)

**Conflict of interest statement:** None.

**References**


