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Impact of polymorphisms of the GGCX gene on maintenance warfarin dose in Chinese populations: Systematic review and meta-analysis

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ABSTRACT

The meta-analysis was conducted to investigate the impact of gamma-glutamyl carboxylase (GGCX) on maintenance warfarin dose. 8 studies were included, focusing on the impact of GGCX single nucleotide polymorphisms (SNPs) on mean daily warfarin dose (MDWD). GGCX (rs699664; AA versus GG, GA versus GG, A versus GG) and GGCX (rs12714145; GA versus GG, AA versus GG, A versus GG) showed no significant differences on mean daily warfarin dose (MDWD). This meta-analysis was the first to report the relationship between GGCX SNPs and MDWD in Chinese populations. No evidence could be found in the relationship between SNPs of GGCX (rs699664 and rs12714145) and maintenance warfarin dose.

Contents

Abbreviations: CI, confidence interval; SD, standard deviation; SNPs, single nucleotide polymorphisms; GGCX, gamma-glutamyl carboxylase; CYP2C9, cytochrome P450 complex subunit 2C9; VKORC1, vitamin K epoxide reductase complex subunit 1; CYP4F2, cytochrome P450 complex subunit 4F2; EPHX1, epoxide hydro-lase 1 INR, International Normalized Ratio; MDWD, mean daily warfarin dose; WMD, weight mean difference.

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Introduction

Warfarin is a coumarin anticoagulant administered via the oral route and is used widely for the treatment of thrombotic diseases. It has a narrow therapeutic window and considerable differences in dosing requirements in different ethnic groups and individuals. Hence, warfarin dose should be given according to the International Normalized Ratio (INR) (van Walraven et al., 2006). Moreover, if dosing is inappropriate, adverse effects such as severe bleeding and recurrence of thromboembolism, especially at the initial treatment phase, can occur (Wysowski et al., 2007).

Several studies have demonstrated that gene polymorphisms are significantly associated with warfarin dose (Lal et al., 2006; Pavani et al., 2012; Rathore et al., 2011). Moreover, meta-analyses have revealed the genes vitamin K epoxide reductase complex subunit 1 (VKORC1), cytochrome P450 complex subunit 2C9 (CYP2C9) and cytochrome P450 complex subunit 4F2 (CYP4F2) to be significantly associated with warfarin dose (Jorgensen et al., 2012; Liang et al., 2011). Recent studies have shown a small-to-moderate significant relationship between the gamma-glutamyl carboxylase (GGCX) genotype and warfarin dose (Chen et al., 2005; Choi et al., 2011; Guo, 2011; Huang et al., 2011; Kimura et al., 2007; King et al., 2010; Krishna Kumar et al., 2014; Liang et al., 2013; Wadelius et al., 2005; Liu YQ, 2013).

GGCX resides in the membranes of endoplasmic reticulum and is composed of 758 amino acids (Suttie et al., 1980). It is located on chromosome 2p12 and spans a genomic region of ≈13 kb consisting of 15 exons (Suttie et al., 1980). GGCX is a key enzyme in the vitamin K cycle. GGCX oxidizes reduced vitamin K to vitamin K-2 and 3-epoxide while adding a carboxyl residue to the gamma carbon on selected glutamic acids; then, functional clotting factors II, VII, IX, and X and other vitamin K-dependent proteins are produced (Gage and Eby, 2004; Rost et al., 2004; Shikata et al., 2004). Researchers revealed the importance of GGCX genes in anticoagulation in 1997 (Wu et al., 1997). In 2004, Shikata et al. (2004) found that polymorphisms in the gene coding for GGCX had a significant impact on warfarin dose. Since then, several studies in various populations have found a significant difference in warfarin doses among diverse GGCX genotypes (Chen et al., 2005; Choi et al., 2011; Guo, 2011; Huang et al., 2011; Kimura et al., 2007; King et al., 2010; Krishna Kumar et al., 2014; Liang et al., 2013; Wadelius et al., 2005; Liu YQ, 2013), but the role of diverse GGCX genotypes is controversial in Chinese population. Carriers of GGCX (rs699664) AA in a Chinese population were believed to need a higher dose of warfarin (Liang et al., 2013), but the opposite result was also found (Guo, 2011). Moreover, the result was indicated that carriers of GGCX (rs12714145) AA required a higher warfarin dose (Huang et al., 2011), but Liu YQ et al. demonstrated that carriers of GGCX (rs12714145) AA required a lower warfarin dose (Liu YQ 2013). In addition, several studies showed no association between polymorphisms in the GGCX gene and warfarin dose (Lou, 2012; Wang et al., 2008; Zhong et al., 2012).