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Impact of CYP2C9, VKORC1 and CYP4F2 genetic polymorphisms on maintenance warfarin dosage in Han-Chinese patients: A systematic review and meta-analysis

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ABSTRACT

Introduction: Warfarin is the most commonly used antithrombotic drug. Single nucleotide polymorphisms (SNPs) of CYP2C9, CYP4F2, VKORC1 1173 and VKORC1-1639 influence warfarin maintenance dosage. We aimed to determine the impact of SNPs of these genes on mean daily warfarin dosage (MDWD) in Han-Chinese patients.

Methods: Strict literature inclusion criteria were established, and literature searching was performed on PubMed, Embase and Cochrane Library for English articles and CNKI, CBM and Wanfang database for Chinese articles before September 2, 2014. Revman 5.3 was used to analyze the relationship between gene SNPs and MDWD in Han-Chinese subjects.

Results: We included 33 studies researching the impact of gene SNPs on MDWD in Han-Chinese subjects. CYP2C9 *3/*3, *1/*3 and *3 carriers needed a 72% (95% confidence interval [CI]: 62.0%–81.0%), 28% (22.0%–33.0%) and 26% (21.0%–32.0%) lower MDWD, respectively, than CYP2C9 *1/*1 carriers. CYP4F2 TT, CT and T carriers required a 18% (7.0%–30.0%), 7% (7.0%–7.0%) and 11% (7.0%–14.0%) higher MDWD, respectively, than CYP4F2 CC carriers. VKORC1 1173 CC, CT and C carriers required a 98% (78.0%–118.0%), 49% (37.0%–62.0%) and 56% (44.0%–67.0%) higher MDWD, respectively, than VKORC1 1173 TT carriers. VKORC1-1639 GG, GA and G carriers needed a 101% (53.0%–149.0%), 40% (36.0%–45.0%) and 38% (35.0%–42.0%) higher MDWD, respectively, than VKORC1-1639 AA carriers.

Conclusions: This meta-analysis is the first to report the relationship between genotypes and MDWD among Han-Chinese patients. The results showed that SNPs of CYP2C9, CYP4F2, VKORC1 1173 and VKORC1-1639 significantly influenced the MDWD in Han-Chinese patients.

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1. Introduction

Warfarin is the most commonly used oral anticoagulant. Its therapeutic window is rather narrow, and its dose must be adjusted according to the international normalized ratio (INR). A high target INR leads to a high risk of bleeding, while embolism events will occur if the target INR is too low. Many clinical and environmental factors, including age, sex, race, body size, co-morbidities and co-medications, as well as gene mutations affect warfarin dose requirements (Xie et al., 2001; Cavallari et al., 2010; Carlquist et al., 2006; Cheng et al., 2009; Klein et al., 2009; Yoshizawa et al., 2009). Cytochrome P450 2C9 (CYP2C9, rs1057910), cytochrome P450 4F2 (CYP4F2, also knew as V433M, rs2108622) and vitamin K epoxide reductase complex subunit 1 (VKORC1, include VKORC1 1173, rs9934438 and VKORC1-1639 also known as 3673, rs9923231) gene polymorphisms are widely considered to be associated with interindividual variations in warfarin dosage.

CYP2C9, VKORC1 and CYP4F2 gene polymorphisms can explain 40%–60% of the variation in interindividual warfarin doses (Klein et al., 2009; Rieder et al., 2005; Krishna Kumar et al., 2014; Lee et al., 2006; Veenstra et al., 2005; Wadelius et al., 2005), while non-genetic factors such as age and sex are considered to account for <15% of this variation (Visscher et al., 2009). The US Food and Drug Administration recommends that genotyping be carried out before the prescription of warfarin in order to improve its therapeutic effect (FDA, 2007).

Several meta-analyses (Sanderson et al., 2005; Lindh et al., 2009a; Yang et al., 2010; Jorgensen et al., 2012; Liang et al., 2012a) have explored the impact of CYP2C9, CYP4F2, VKORC1 1173 and VKORC1-1639 gene polymorphisms on mean daily warfarin dosage (MDWD) in Caucasian, African and Asian subjects. As the first meta-analysis of the impact of gene polymorphism warfarin dosage requirement, Sanderson et al. (2005) included 19 studies in their research and found that patients with CYP2C9*2 and CYP2C9*3 alleles need lower MDWD than wild-type homozygotes CYP2C9*1*1. Subsequently, Lindh et al., (2009a) and Jorgensen et al., (2012) also the drew similar conclusions by conducting meta-analysis separately. Yang et al. (2010) found that the impacts of gene polymorphism on warfarin dosage requirement were significantly different between Caucasian and Asian population. Patients with VKORC1 1173 CTand 1173 CC required 44% (95% CI, 32%, 56%) and 97% (95% CI, 73%, 122%) higher MDWD than 1173 TT carriers. VKORC1-1639GA and -1639 GG carriers required 52% (95% CI, 41%, 64%) and 102% (95% CI, 85%, 118%) higher MDWD than -1639AA carriers. Liang et al. (2012a) reported that carriers of CYP4F2 CT, TT genotypes required 10.0% (95% CI, 4.0–15.0) and 21.0% (95% CI, 9.0–33.0) higher warfarin doses than homozygous CC respectively. Although genetic associations with warfarin response vary between ethnicities, but most of the previous meta-analyses were conducted by including Caucasian, African and Asian subjects.

However, no such meta-analysis has been conducted of studies involving only Han-Chinese subjects. Such an analysis is required because the size of the Han-Chinese population is up to 1.37 billion (M-S Wen.pdf). We therefore conducted a systematic review and meta-analysis to clarify the relationship between gene polymorphisms and MDWD in the Han-Chinese, and to determine which genotype must be tested for before prescribing warfarin. Our study includes 33 papers published in recent years about CYP2C9, CYP4F2, VKORC1 1173 and VKORC1-1639 gene polymorphisms in the Han-Chinese.

2. Medthods

2.1. Search strategy

We searched the PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) and Wanfang databases for articles published before September 2, 2014. Print periodicals were also searched. The literature search was limited to studies published in English and Chinese. Studies written in English were searched for on the Cochrane Library, PubMed and Embase databases, and studies written in Chinese were searched for on the CNKI, CBM and Wanfang database or identified through the print periodical search. The keywords were warfarin (MeSH Terms) and Chinese (MeSH Terms) plus any of the following terms: genes (MeSH Terms, mutation (MeSH Terms), polymorphisms (MeSH Terms), Genetic Polymorphism (MeSH Terms), pharmacogenetics (MeSH Terms), CYP2C9 (MeSH Terms), CYP4F2 (MeSH Terms), VKORC1 (MeSH Terms), VKORC1 1173 (Free Terms) and VKORC1-1639 (Free Terms). Corresponding Chinese medical terms were used when we searched on CNKI databases for literatures written in Chinese.

2.2. Study selection

To be included, studies had to meet the following criteria: (1) patients received warfarin treatment, (2) patients were Han-Chinese, (3) at least one of the four target genes was tested and (4) warfarin maintenance dosage was mentioned along with the target gene(s). There were no special limits on INR range, patient characteristics (diseases, age, weight and height) and use of other drugs.

2.3. Data extraction

The research data were extracted and sorted by two reviewers (Chen CM and Chen ZJ) independently. Information such as year of publication, location (province or city), disease types, target INR, gene frequencies (wild type and variant type) and average warfarin maintenance dosage was extracted from the selected studies. Then, the two reviewers checked the integrity and accuracy of the extracted data, and resolved any differences or common points of confusion by discussion. In case of disagreements, other researchers read the literature and decided whether or not to include the study. If there was unclear or missing information in any of the studies, we were to contact the authors via phone or e-mail to obtain additional information.

2.4. Study quality assessment

We applied the checklist recommended by the Cochrane handbook (Julian and Green, 2011) as well as other methods recommended in related literature (Little et al., 2002; Jüni et al., 1999) to assess the quality of the selected papers: (1) study purpose, (2) validity of genetic analysis, including type of study sample, time of sample collection, definition of each genotype and genotyping methods used, (3) subject selection, including geographic area from which the subjects were recruited, subjects' age (mean age and standard deviation or age range), sex ratio, and (4) statistical issues, e.g., number of subjects included and analysis method.