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SHORT COMMUNICATION

Genetic Variability of SNP rs7089580 in Latin American populations and its impact on Warfarin dosage

Variabilidad Genética del SNP rs7089580 en poblaciones latinoamericanas y su impacto en la dosificación de Warfarina

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ABSTRACT

Introduction: genetic variability in genes that encode drug metabolizing enzymes can influence the response to medications and the doses necessary for an adequate therapeutic effect. In the case of warfarin, a widely used anticoagulant, the enzyme CYP2C9 is responsible for metabolizing its active enantiomer, S-warfarin.
Method: the frequencies of the T allele of the SNP rs7089580 were analyzed in Latin American populations using data from the 1000 Genomes Project. Tools such as VCFtools were used to determine the frequency of the T allele and the Hardy-Weinberg equilibrium (HW) and linkage disequilibrium (LD) between the SNP rs7089580 and the promoter SNP rs12251841 of the CYP2C9 gene were evaluated.
Results: the frequencies of the T allele vary significantly between populations, with the Puerto Rican population presenting the highest frequency (17 %) and the Peruvian population the lowest (4 %). The results show that Latin American populations are in HW equilibrium, suggesting stability in genetic frequencies.
Conclusions: the variability in the frequency of the T allele of the SNP rs7089580 in Latin American populations reflects the complex genetic mix of the region. The balance of HW and the strong linkage disequilibrium between the SNPs suggest that rs7089580 may be a useful marker to predict CYP2C9 expression and response to warfarin.

Keywords: SNP rs7089580; Warfarin Dosage; Genetic Variability; Latin American Populations; Personalized Medicine.

RESUMEN

Introducción: la variabilidad genética en los genes que codifican enzimas de metabolización de drogas puede influir en la respuesta a los medicamentos y en las dosis necesarias para un efecto terapéutico adecuado. En el caso de la warfarina, un anticoagulante ampliamente utilizado, la enzima CYP2C9 es responsable de metabolizar su enantiómero activo, S-warfarina.
Método: se analizaron las frecuencias del alelo T del SNP rs7089580 en poblaciones latinoamericanas utilizando datos del Proyecto 1000 Genomes. Se utilizaron herramientas como VCFtools para determinar la frecuencia del alelo T y se evaluó el equilibrio de Hardy-Weinberg (HW) y el desequilibrio de enlace (LD) entre el SNP rs7089580 y el SNP promotor rs12251841 del gen CYP2C9.
Resultados: las frecuencias del alelo T varían significativamente entre las poblaciones, con la puertorriqueña presentando la frecuencia más alta (17 %) y la peruana la más baja (4 %). Los resultados muestran que

las poblaciones latinoamericanas están en equilibrio de HW, lo que sugiere estabilidad en las frecuencias genéticas.
Conclusiones: la variabilidad en la frecuencia del alelo T del SNP rs7089580 en poblaciones latinoamericanas refleja la compleja mezcla genética de la región. El equilibrio de HW y el fuerte desequilibrio de enlace entre los SNPs sugieren que rs7089580 puede ser un marcador útil para predecir la expresión de CYP2C9 y la respuesta a la warfarina.

Palabras clave: SNP rs7089580; Dosificación de Warfarina; Variabilidad Genética; Poblaciones Latinoamericanas; Medicina Personalizada.

INTRODUCTION

Genetic variation in genes encoding drug-metabolizing enzymes can influence drug response and the doses required for an adequate therapeutic effect. In the case of warfarin, a widely used anticoagulant, the enzyme CYP2C9 is responsible for metabolizing its active enantiomer, S-warfarin.[1] Alleles in the CYP2C9 gene, such as CYP2C92 and CYP2C93, are associated with reduced enzymatic activity and, therefore, a lower dose requirement.[2,3] These variants, however, are less frequent in African populations and explain less of the variability in warfarin dose compared to Caucasian and Asian populations.[4] In addition to CYP2C9, the VKORC1 gene also plays a role in warfarin dose variability. Variants in VKORC1 can alter sensitivity to warfarin, affecting the dose needed to achieve the desired effect.[5] These findings indicate that genetic diversity among populations is an important factor in optimizing warfarin therapy and minimizing the risk of adverse events.

The single nucleotide polymorphism (SNP) rs7089580 in the CYP2C9 gene has been identified as an important genetic marker in the variability of warfarin dose in African American patients. This SNP is associated with higher CYP2C9 mRNA expression and increased S-warfarin clearance, resulting in a higher dose requirement in carriers of the T allele.[6] Studies have shown that rs7089580 is in complete linkage disequilibrium with the promoter SNP rs12251841, providing a biologically plausible explanation for the observed increase in CYP2C9 expression levels.[4] Additionally, incorporating rs7089580 into dosing algorithms specific to African Americans has improved the accuracy in predicting high warfarin doses in this population compared to traditional algorithms.[7]

The aim of this study is to analyze the frequency of the SNP rs7089580 in global populations, with an emphasis on Latin America, considering their recent mixed ancestry, which includes contributions from East Asia, Europe, and Africa, the latter being less intense. Understanding the frequency of this SNP can provide valuable information to optimize warfarin dosing and improve the safety and efficacy of anticoagulant treatment in these populations.[8] Furthermore, considering the region-specific genetic diversity, this study can help develop more precise and personalized dosing algorithms.[4,7]

METHOD

To analyze the frequency of the T allele of SNP rs7089580 and its relationship with the promoter SNP rs12251841 of the CYP2C9 gene in Latin American populations, the 1000 Genomes Project database was used.[9] This project provides dense and diverse genomic data, allowing for a comprehensive analysis of genetic variants in different populations.

Genomic data for Latin American populations were downloaded from the 1000 Genomes Project in VCF (Variant Call Format). The populations included in the analysis and their respective sample sizes were as follows: Mexicans in Los Angeles, California (MXL, n=64), Puerto Ricans in Puerto Rico (PUR, n=104), Colombians in Medellin, Colombia (CLM, n=94), and Peruvians in Lima, Peru (PEL, n=85).

To determine the frequency of the T allele of SNP rs7089580 in each population, the VCFtools software was used. Additionally, Hardy-Weinberg equilibrium (HW) was assessed for SNP rs7089580, and linkage disequilibrium (LD) between SNP rs7089580 and the promoter SNP rs12251841 of the CYP2C9 gene was examined.

RESULTS

The frequencies of the T allele of SNP rs7089580 vary notably among non-American macro populations. In African populations (AFR), the frequency is high, with Gambians in Western Division (GWD) showing 22,1 % and Yoruba in Ibadan, Nigeria (YRI) 22,7 %. East Asian populations (EAS) show very low frequencies, such as Japanese in Tokyo (JPT) with 0,5 % and Kinh in Ho Chi Minh City, Vietnam (KHV) with 2,0 %. In South Asia (SAS), the frequencies are intermediate, with Bengalis in Bangladesh (BEB) at 11,0 % and Indian Gujarati in Houston, Texas (GIH) at 13,6 %. In Europe (EUR), frequencies are high, with British in England and Scotland (GBR) at 23,1 % and Finns (FIN) at 21,7 %.

In American populations (AMR), the frequency of the T allele also shows variability. Colombians from Medellin, Colombia (CLM) have a frequency of 12,8 %, while Mexican Ancestry in Los Angeles, USA (MXL) have

11,7 %. Puerto Ricans from Puerto Rico (PUR) have a frequency of 17,3 %, and Peruvians in Lima, Peru (PEL) show one of the lowest frequencies within this macro population, at 4,1 % (figure 1).

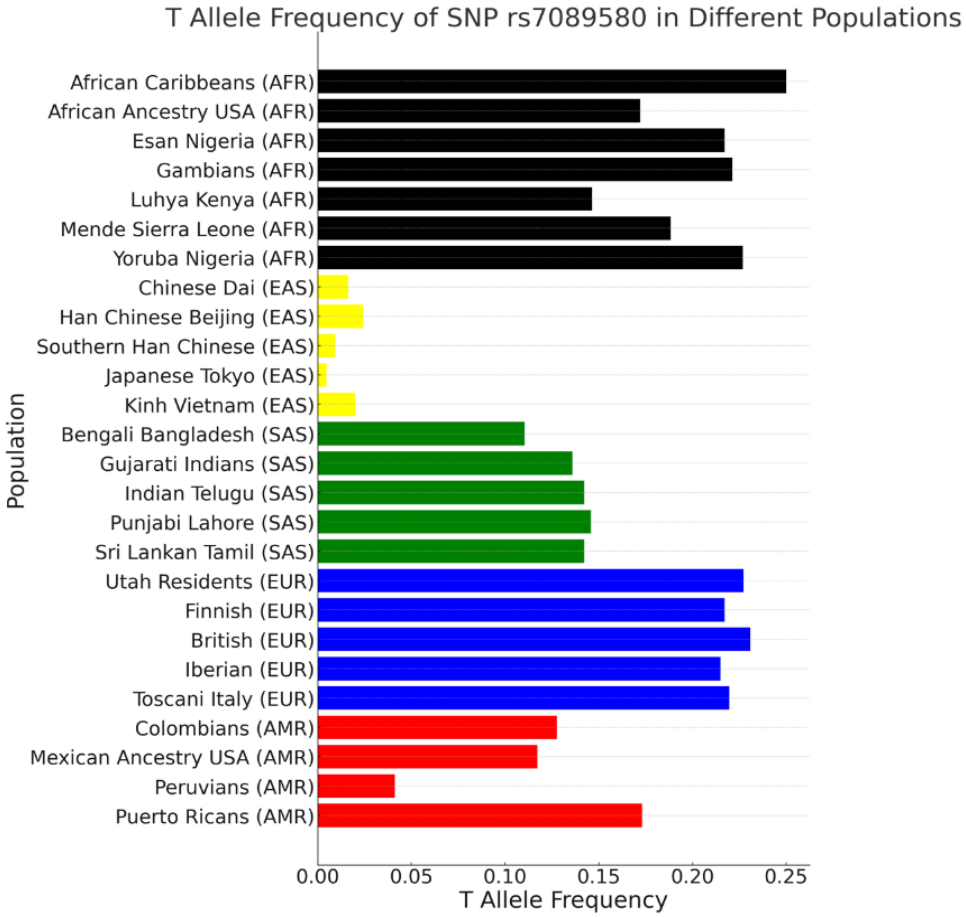

Figure 1. Frequency of the allele CYP2C9 rs7089580T

The analysis of Hardy-Weinberg equilibrium (HW) for SNP rs7089580 reveals that globally the population is not in equilibrium ($p < 0,05$), indicating possible influences of evolutionary factors such as natural selection or migration. At the macro population level, African (AFR) and South Asian (SAS) populations show significant disequilibrium ($p < 0,05$), while East Asian (EAS), European (EUR), and American (AMR) populations are in HW equilibrium ($p < 0,05$). Within the 26 individual populations, the majority are in HW equilibrium. In Latin America, the populations are in HW equilibrium. Regarding linkage disequilibrium, our analysis confirms LD between SNP rs7089580 and the promoter SNP rs12251841. At the global level, the correlation between the two SNPs was R2= 0,98, while at the macro population level, it ranged from R^2= 0,97 (Africa) to R^2= 1 (America).

DISCUSSION

The results of this study show high variability in the frequency of the T allele of SNP rs7089580 in different global populations, including Latin American populations. This finding is consistent with previous studies showing that genetic diversity influences warfarin response and the doses required to achieve an adequate therapeutic effect.[4,7]

In Latin American populations, the frequency of the T allele varies widely, with Puerto Ricans presenting the highest frequency (17 %) and Peruvians the lowest (4 %). This variability is consistent with the genetic admixture of Latin American populations, influenced by ancestral contributions from Europe, Africa, and East Asia, with the Peruvian population having a greater component of Native American ancestry, which deriv Francisco Javier Quintero,es from ancestral East Asian populations, while the Puerto Rican population has a greater European component.[10] This is consistent with the observations of Takahashi and Echizen[3] and Perera et al.[4] on genetic diversity and its impact on warfarin dosing.

The Hardy-Weinberg equilibrium (HW) in Latin American populations suggests that there are no significant micro-evolutionary forces affecting the frequency of SNP rs7089580, indicating stability in frequencies, which can be considered when developing personalized dosing algorithms.[5] The linkage disequilibrium (LD) between SNP rs7089580 and the promoter SNP rs12251841 of the CYP2C9 gene, both globally and in each of the five

macro populations, coincides with previous research highlighting the relevance of these SNPs in warfarin dose variability.[4,6] This strong LD indicates that rs7089580 can be an effective marker for predicting CYP2C9 expression and, consequently, warfarin response.

The variability in the frequency of the T allele in Latin American populations is significant, and this study suggests the need to expand samples from Latin American populations to obtain a more complete view of the distribution of SNP rs7089580 and other relevant genetic markers, to improve the safety and efficacy of anticoagulant treatment in this subcontinent.[3,4,7]

This study has some limitations. The sample size may not capture all the genetic variability of Latin American populations and focusing on only four populations may not fully represent the region's diversity. Additionally, data from the 1000 Genomes Project, although inclusive, may not fully reflect clinical conditions.

CONCLUSIONS

The frequency of the T allele of SNP rs7089580 varies significantly among Latin American populations, reflecting the region's complex genetic admixture.

The Hardy-Weinberg equilibrium in these populations suggests stability in genetic frequencies, which is relevant for developing personalized dosing algorithms.

The strong linkage disequilibrium between SNP rs7089580 and the promoter SNP rs12251841 reinforces the utility of rs7089580 as a marker for predicting warfarin response.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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