Homozygosity for the HR2 Haplotype: Is It a Risk Factor for Thrombosis?

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ABSTRACT

A4070G (His 1299 Arg) polymorphism in exon 13 of factor V gene can influence factor V levels and contribute to the activated protein C resistance. We are presenting our data concerning Turkish population and postulate that homozygosity for the HR2 haplotype may be an important risk factor for thrombosis.

Key Words: Haplotype, HR2, Polymorphism, A4070G, Thromboembolism.

ÖZET

HR2 Haplotipi İçin Homozigotluk: Tromboz İçin Bir Risk Faktörü mü?

HR2 haplotipinde bulunan A4070G (His 1299 Arg) polimorfizmi faktör V geninde yer alır ve plazma faktör V düzeylerini etkileyerek aktif protein C direncine yol açabilir. Bu çalışmada Türkiye verisi sunulmakta ve HR2 haplotipinde homozigotluğun tromboz için risk faktörü olabileceği hipotezi sunulmaktadır.

Anahtar Kelimeler: Haplotip, HR2, Polimorfizm, A4070G, Tromboembolizm.

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INTRODUCTION

HR2 haplotype includes an A4070G (His1299Arg) polymorphism in exon 13 of the factor V gene which replaces His (R1 allele) by Arg (R2 allele) at position 1299 of the B domain. This haplotype was shown to influence plasma factor V levels and contribute to the activated protein C resistance (APCR) phenotype. This haplotype was found to be frequent in healthy individuals. Thrombotic risk of this polymorphism is controversial according to several studies even also for the homozygote HR2 individuals[1-10]. Plasma samples from these individuals contain an increased ratio of the more highly glycosylated and more thrombogenic isoform of factor

V (V1), which is a more potent co-factor for thrombin generation, and a less potent co-factor for APC-mediated inactivation of factor VIIIa in vitro[11]. As homozygous HR2 haplotype is rare, we compiled and present our data concerning Turkish population.

METHODS

Amplification of exon 13 of the factor V gene was performed by polymerase chain reaction with the use of the primers of 5'-CAAGTCCTTCCCCACAGATATA-3' and 5'-GGTTACTTCAAGGACAAAATACCTGTAAAGCT-3', with an annealing at 57°C. Amplified 703 bp fragment was restricted with Rsa I restriction endonuclease enzyme (Promega, Madison, USA). A normal/noncarrier individual carried only a 492 bp fragment, a heterozygous individual carried a 492 bp with a 211 bp fragment and a homozygous individual carried only a 211 bp fragment[1,5].

RESULTS

Fourhundredandnintythree individuals with thrombosis (arterial or venous) and 112 individuals without any familial history of thrombosis from the same geographic area with the same age range were included after obtaining a written consent from each individual. Total of four homozygous HR2 haplotype individuals were determined (OR= 0.45, Cl: 0.082-2.5, p= 0.691). Two of the homozygous patients were in pediatric age range [2/314 (0.6%)]. Both were found also to carry prothrombin 20210 A mutation. Two of the pediatric patients had cerebral infarct.

Two of the patients had pulmonary embolism (2/179; 1.1%) one of them was also carrying PT20210A.

Other R2R2 individual was 30 years old and did not experienced thrombosis, which was not included to the study group, had two family members with the diagnosis of early myocardial infarction. We were not able to analyse his family members. One of the controls (1/112; 0.9%) had homozygous HR2. Clinical and molecular analysis of these cases are given in Table 1.

Table 1. Clinical data and molecular analysis of the HR2 haplotypes

Patient	Age	Diagnosis	FVL	PT 20210
Female	54	Pulmonary embolism	G/G	G/G
Male	48	Pulmonary embolism	G/G	G/A
Male	30	Familial thrombosis	G/G	G/G
Female	2	Stroke	G/G	G/A
Female	3	Stroke	G/G	G/A
Female	16	Control	G/G	G/G

DISCUSSION

Although rare, homozygosity for the HR2 haplotype may be an important risk factor for thrombosis. The risk seems to be higher in patients with other genetic risk factors. Further studies are warranted to confirm this hypothesis.

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