Factor V Leiden G1691A and factor II G20210A point mutations and pregnancy in North-West of Iran

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Factor V Leiden G1691A and factor II G20210A point mutations and pregnancy in North-West of Iran

Morteza Bagheri · Isa Abdi Rad · Fariba Nanbakhsh

Abstract

**Purpose** The roles of several hereditary predispositions for venous thromboembolism have been evaluated in women with habitual abortion. We studied the prevalence of FV Leiden G1691A and FII G20210A mutations in women with habitual abortion and healthy controls.

**Methods** 60 unrelated fertile females, as controls, and 70 unrelated women with at least three consecutive pregnancy losses entered at the present study. MAS-PCR was carried out for detection of FV Leiden G1691A and FII G20210A mutations.

**Results** FV Leiden G1691A mutation was not found in the studied cases and controls, that is, all of the cases and the controls had normal FV Leiden 1691GG genotype. FII 20210AA genotype was not found in any of patients or controls. 2.5% of alleles (3 out of 120 chromosomes) in controls and 15.714% of alleles (22 out of 140 chromosomes) in cases had FII 20210A mutation. The FII G20210A allele frequency was 0.157 in cases and 0.025 in controls. Regarding FII G20210A mutation, the distribution of GG, GA and AA genotypes were 48 (68.57%), 22 (31.43%) and 0 (0%) in the cases and 95 (95%), 5 (5%) and 0 (0%) in the controls, respectively. Significant differences in both FII G20210A alleles and FII G20210A genotypes frequencies were observed in the cases versus the controls.

**Conclusion** FII G20210A mutation is significantly associated with habitual abortion.

**Keywords** Factor V Leiden · Coagulation factor II · Pregnancy loss

Introduction

Habitual abortion (HA) is defined as at least three consecutive spontaneous pregnancy losses that occur before 20 weeks’ gestation [1]. HA is known as a heterogeneous disease and the etiology of HA remains unexplained, however, the role of anticoagulants in the prevention of HA cannot be ruled out [1, 2]. Hereditary and acquired risk factors play important roles in thromboembolism which can result some problems during pregnancy [3]. Interaction of genetic background and environmental factors could result in venous thromboembolism [4]. Factor V Leiden (FV Leiden) and prothrombin gene mutations are common hereditary risk factors for venous thromboembolism [4, 5]. Results of Coulam et al. [6] implied that multiple thrombophilic gene mutations rather than specific gene mutations have been associated with recurrent miscarriage [6]. In most of the cases, transition of G to A at nucleotide position 1691 of the factor V gene leads to production of a defective factor V (Factor V Leiden) that is associated with resistance to activated protein C [7], and also transition of G to A at nucleotide position 20210 of the 3’ un-translated region of the prothrombin gene associated with high levels of plasma prothrombin [8]. FV Leiden and factor II (FII) G20210A mutations are associated with increased production of...
thrombin and risk of venous thrombosis [9]. Hypercoagulation state predisposes individuals to complications in pregnancy, e.g. pre-eclampsia and HA [10, 11]. It has been demonstrated that FV Leiden G1691A and FII G20210A mutations are independent risk factors for venous thromboembolism [12]. The results of several investigations show that FV Leiden G1691A and FII G20210A mutations are associated with unexplained recurrent miscarriages [13–22]. But, some others found no association [23–26]. The present case–control study was conducted to evaluate the FV Leiden G1691A and FII G20210A mutations in women with a history of three or more consecutive pregnancy losses and healthy controls.

Methods

Ethics approval was obtained from Urmia University of Medical Sciences. This case–control study was carried out in Motahari Hospital (Urmia, Iran), an Obstetrics and Gynecology referral hospital, from March 2008 through September 2010. 60 healthy fertile unrelated females (controls) with age range of 20–38 years (mean 29.41 ± 5.01 years) and 70 unrelated women with a history of three or more consecutive pregnancy losses (cases) with age range of 18–40 years (mean 27.62 ± 5.37 years) were entered at study. Considering the age and BMI, there was no significant difference between cases and controls (P value >0.05). Controls had a history of two or more successful live births. All cases had a history of three or more consecutive spontaneous pregnancy losses that occurred before 20 weeks’ gestation. Participants with a history of three or more consecutive pregnancy losses that occurred before 20 weeks’ gestation. Participants with a history of fetal demise in two or more consecutive spontaneous pregnancy losses and healthy controls.

Results

Figure 1 shows the frequencies of FII 20210G/A alleles and genotypes in cases and controls. We have studied 260 chromosomes (60 unrelated-females and 70 cases) from Azeri Turkish origin for the presence or absence of FV Leiden G1691A and FII G20210A mutations. FV Leiden G1691A mutation was not found in the studied cases and controls. FII 20210AA genotype was also not found in any case of patients or controls group. 2.5% of alleles (3 out of 120 chromosomes) in controls and 15.714% of alleles (22 out of 140 chromosomes) in cases had FII 20210A mutation. The FII G20210A allele frequency was 0.157 in cases and 0.025 in controls. Regarding FII G20210A mutation, the distribution of GG, GA and AA genotypes were 48 (68.57%), 22 (31.43%) and 0(0%) in cases and 95 (95%), 5 (5%) and 0 (0%) in controls.
In the present study, FII G20210A allele distributions of the cases ($\chi^2 = 2.433 < 3.84$, $P$ value = 0.296 > 0.05) and controls ($\chi^2 = 0.039 < 3.84$, $P$ value = 0.980 > 0.05) were in agreement with the expected distribution (Hardy–Weinberg equilibrium) by the Chi-square test with 2 degree of freedom. Significant differences in both FII G20210A alleles and FII G20210A genotypes frequencies were observed in cases versus controls (see Table 1). But this does not refer to FV Leiden G1691A alleles and genotypes. Figure 2 is a representative image of the gels.

**Discussion**

Venous thrombosis is defined as a multifactorial disease and results from compound interaction of inherited abnormalities of blood coagulation process and acquired risk factors [30]. This is the first study that investigated the FV Leiden G1691A and FII G20210A alleles and genotype distributions in the Iranian Azeri Turkish females with habitual abortion. The findings of the present study showed that the FV Leiden mutant allele “FV Leiden 1691A” was not found in any of our cases and controls. Our results failed to determine any association between FV Leiden G1691A mutation and HA. This finding is in agreement with several studies [23–26, 31], but are inconsistent with some others [13–22]. In the present study, 2.5% of alleles in the controls and 15.7% of alleles in the cases had FII 20210A mutation which implies that the FII G20210A allele was significantly higher among the cases (2.5 vs. 15.7%). Our finding is consistent with many studies [14, 16, 20, 21], but it is inconsistent with Behjati et al. [32] study. The high prevalence of FII 20210A mutation in the studied population indicates that screening for FII 20210A mutation should be considered for detection of high risk patients. The limitation of the present study is that cases and controls are not precisely matched considering number of contributors. Therefore, studies of cases and healthy controls in a cohort of large and matched sample size are necessary to analyze more details in the studied population and management of high risk carriers.

**Table 1** FII 20210G/A alleles and genotypes frequencies in cases and controls

<table>
<thead>
<tr>
<th>FII 20210G/A allele/genotype</th>
<th>Cases F (%F)</th>
<th>Controls F (%F)</th>
<th>OR (95% CI)</th>
<th>Uncorrected: Yates-corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>48 (68.571)</td>
<td>57 (95)</td>
<td>0.11 (0.03–0.44)</td>
<td>14.53 0.0001</td>
</tr>
<tr>
<td>GA + AA</td>
<td>22 (31.429)</td>
<td>3 (5)</td>
<td>8.71 (2.27–39.08)</td>
<td>12.88 0.0003</td>
</tr>
<tr>
<td>G</td>
<td>118 (84.286)</td>
<td>117 (97.5)</td>
<td>0.14 (0.03–0.50)</td>
<td>12.98 0.0003</td>
</tr>
<tr>
<td>A</td>
<td>22 (15.714)</td>
<td>3 (2.5)</td>
<td>7.27 (1.99–31.41)</td>
<td>11.51 0.0006</td>
</tr>
</tbody>
</table>

**Fig. 1** Frequencies of FII 20210G/A alleles and genotypes in cases and controls

**Fig. 2** Detection of FV Leiden G1691A and FII G20210A mutations by MAS-PCR. FV Leiden G1691A mutation results in a PCR product of 150 bp and FII G20210A mutation produces a 340 bp fragment. Two PCR reactions have been carried out for each sample, first lane with mutant allele, and the second lane with normal allele. PCR reactions of six samples have been shown in the figure. [e.g., lanes 1 and 2 are from a person without mutations with two normal bands, and lanes 5 and 6 are from a person who is heterozygote for FII (PT), and normal for FV]. Lane M DNA ladder (50 bp)
Conclusion

FII G20210A mutation is significantly associated with HA in tested population.

Acknowledgments

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Conflict of interest

I declare that there is no conflict of interest with any others but the authors, and also the article has not been sent to any journals at the same time.

References