

The relationship between gene polymorphisms of coagulation factors II, V and XI and risk of recurrent pregnancy loss in Palestine

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ABSTRACT

This retrospective case-control study was carried out in order to investigate the association between *Factor II* (G20210A), *Factor V* (G1691A, H1299R, Y1702C) and *Factor XI* (rs3756008 A>T) gene polymorphisms and recurrent pregnancy loss (RPL) in a group of Palestinian women residing in Gaza strip. A total of 400 females, 200 RPL patients and 200 women without previous history of RPL, aged 20 to 35 years were included in the study. *Factor V* (G1691A) and *Factor II* (G20210A) polymorphisms were analyzed by allele-specific PCR whereas, *Factor V* (H1299R, Y1702C) and *Factor XI* (rs3756008 A>T) gene polymorphisms were screened by PCR-RFLP. No statistically significant difference existed between RPL cases and controls in terms of the allelic and genotypic distribution of *Factor II* (G20210A), *Factor V* (Y1702C) or *Factor XI* (rs3756008 A>T). On the other hand, the minor allele of the two *Factor V* gene polymorphisms (G1691A and H1299R) independently showed statistically significant association with RPL. *Factor V* G1691 and H1299R polymorphisms may increase the risk for RPL in Gaza strip women, and should be screened for in cases suspected to have inherited thrombophilia.

Keywords: *Factor V*, *Factor II*, *Factor XI*, gene polymorphism, recurrent pregnancy loss.

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INTRODUCTION

Pregnancy is associated with major changes in many aspects of homeostasis all contributing to maintain placental function and to prevent excessive bleeding during delivery (Prisco et al., 2005).

Recurrent miscarriage is the occurrence of two or more consecutive pregnancy losses during the first trimester, and accounts for up to 5% of clinically recognized pregnancy losses (Branch et al., 2010). This is a devastating problem, particularly to Palestinian families who are fond of having large families. Despite extensive research to explain the causative effects of recurrent pregnancy loss (RPL), in about 50% of the cases the cause(s) remain idiopathic (Kovalevsky et al., 2004).

RPL has many possible causes that can be categorized as genetic abnormalities, hormonal and metabolic disorders, uterine anatomic abnormalities, infectious causes, immune disorders and thrombophilic disorders (Rull et al., 2012).

Thrombophilia can be defined as a predisposition to

form clots inappropriately. Thrombotic events are increasingly recognized as a significant source of mortality and morbidity (Khan and Dickerman, 2006) and women with thrombophilia have been shown to be at an increased risk of pregnancy loss and possibly other serious obstetric complications (Kujovich, 2004).

The most common cause of acquired thrombophilia is antiphospholipid antibodies. Inherited thrombophilias, on the other hand, can result from inter-individual variation in genes involved in the various aspects of thrombus formation. Inherited thrombophilia is further grouped into; inherited defects of coagulation (e.g., Factor V Leiden, Factor II Prothrombin, Fibrinogen, Factor XIII), inherited defects of fibrinolysis (e.g., Plasminogen activator inhibitor-1 (PAI-1)), inherited defects of enzymatic pathway in relation to development of venous thromboembolism (VTE) and inherited defects of platelets and thrombosis (e.g., Human Platelet Antigen-1 "HPA-1"; Methylene tetrahydrofolate reductase "MTHFR")

Table 1. Demographic data of RPL patients compared to controls.

Parameter	RPL patients (n = 200)	Control (n = 200)	P-value
Age (years)	26.1 ± 6.3	27.2 ± 5.8	NS*
Body mass index (kg/m ²)	24.9 ± 0.9	23.8 ± 0.7	NS
Number of abortions	2.7 ± 0.8	-	-

NS: not significant.

Table 2. PCR primers used in genotyping the polymorphisms.

Gene	Primer sequence	Reference
Factor II (G20210A)	Common 5'- TCTAGAAACAGTTGCCTGGCAG-3'	Gawish et al. (2013)
	Mutant 5'- GCACTGGGAGCATTGAGGATT-3'	
	Normal 5'- GCACTGGGAGCATTGAGGATC-3'	
Factor V (G1691A)	Common 5'-CTTTCAGGCAGGAACAACACC-3'	Dajani et al. (2012)
	Mutant 5'-TGGACAAAATACCTGTATACCTT-3'	
	Normal 5'-GGACAAAATACCTGTATTGCTC-3'	
Factor V (A4070G)	F 5'-TGCTCCTTTATCTCCGAGGACC-3'	Torabi et al. (2009)
	R 5'-CTCTGGAGGAGTTGATGTTTGTCC-3'	
Factor V (A5279G)	F 5'-CTGTGCGGGCTTGGGTCT-3'	Torabi et al. (2009)
	R 5'-GAAATAACCCCGACTCTTC-3'	
FXI rs3756008 (A>T)	F 5'-TTTGGTTTTCCAGTGAAGCA-3'	This study
	R 5'-GTGCCAAGAATGGCTTTCA-3'	

(Konecny, 2009).

Due to their important roles in the coagulation pathway, this study was designed in order to test whether *Factor V* (G1691A, H1299R, Y1702C), *Factor II* (G20210A) and *Factor XI* (rs3756008 A>T) gene polymorphisms are associated with RPL in Palestinian women.

MATERIALS AND METHODS

Study population

The study population consisted of 400 women from Gaza strip. The patient group consisted of 200 women between 20 and 35 years who had at least two consecutive unexplained RPL at ≤20 weeks of gestation. Patients who had intermarriage were excluded. The control group consisted of 200 women who had at least two live births without previous history of abortion. The control and patient groups were matched in age and all other possible characteristics. Table 1 summarizes the demographic characteristics of the two groups.

Informed consent was obtained from all participants, and approval for conducting the study was obtained from the local ethics committee.

DNA extraction and evaluation of polymorphisms

The DNA was isolated from whole blood samples using Wizard DNA extraction kit (Promega, USA) as described by the

manufacturer. The isolated DNA was stored at -20°C until the analysis of genetic polymorphisms.

Factor V G1691A (R506Q; rs6025) polymorphism was analyzed by allele-specific PCR (AS-PCR) using the primers described in Table 2. The PCR conditions were as described by Dajani et al. (2012). The 233 bp PCR products were resolved on ethidium-bromide stained 3% agarose gel.

Factor V H1299R (R2; A4070G) polymorphism was analyzed by polymerase chain reaction (PCR)-restriction fragment length polymorphism (PCR-RFLP) method using the primers presented in Table 2. The PCR conditions were as described by Torabi et al. (2009). The PCR product (1613bp) was digested using RsaI restriction enzyme (NEB, UK) which cuts the wild type allele into two segments (1483bp and 130bp) but cuts the mutant allele into three segments (862+576+130bp). Heterozygotes therefore, should produce four fragments: 1483, 862, 576 and 130bp. The three genotypes were distinguished from each other by running the enzyme digestion PCR products on 2% agarose gel.

Factor V A5279G (Y1702C) polymorphism was examined by PCR-RFLP following the method of Torabi et al. (2009). The PCR primers presented in Table 2 should yield a product of 120bp. When digested with restriction enzyme *AccI* (NEB, UK), the A-allele product remains uncut whereas, that of the polymorphic G-allele is cut into two fragments of 105 and 15bp. The results were visualized by electrophoresis on 3% agarose gel.

Factor II G20210A polymorphism was determined by allele-specific PCR using the primers shown in Table 2 and as described by Gawish and Al-Khamees (2013). The 340bp product was detected by electrophoresis using 3% agarose gel.

Factor XI rs3756008 (A>T) polymorphism was analyzed by PCR-RFLP using the primers shown in Table 2 and *MluCI* restriction

enzyme. The PCR primers were designed using the freely available Primer3web (<http://primer3.ut.ee/>) software. When digested with MluCI (NEB, UK), the PCR product (194bp) remains intact if A-allele is present and, yields two fragments (131 and 63bp) for the polymorphic T-allele. PCR-RFLP products were resolved on 3% agarose gel.

Statistical analysis

The genotype, allele frequency in RPL patients and the controls were analyzed by standard Chi-square test and odds ratio (OR) for risk of RPL at 95% confidence intervals (CI) were calculated. All statistical analyses were performed using the SPSS 17.0 software package (SPSS, Chicago, USA). Hardy-Weinberg equilibrium (HWE) was tested using a freely available software (<http://www.oege.org/software/hwe-mr-calc.shtml>).

RESULTS

Genotypic and allelic distribution of the investigated polymorphisms in RPL patients and controls

The genotypic and allelic frequencies of the study population are shown in Table 3. Statistical analyses revealed that no statistically significant differences existed between RPL patients and controls in terms of *Factor II* (G20210A), *Factor V* (Y1702C) or *Factor XI* (rs3756008 A>T). On the other hand, the minor allele of the two *Factor V* gene polymorphisms (G1691A and H1299R) showed statistically significant association with RPL.

Hardy-Weinberg equilibrium

With the exception of the genotypes of *Factor XI* (rs3756008 A>T) polymorphism, genotypes frequencies of the other four investigated polymorphisms were in Hardy-Weinberg equilibrium (HWE).

Independent effects of *Factor V* (G1691A) and (A4070G) polymorphisms

In order to verify the independent effect of G1691A and A4070G polymorphisms on RPL, the three samples in which both polymorphisms coexisted were excluded and the allele frequencies were recalculated. The frequency of the minor allele of each of the two polymorphisms remained significantly different between the RPL and controls.

DISCUSSION

The present study focused on the polymorphisms in *Factor V*: G1691A, H1299R, Y1702C; *Factor II* G20210A, and *Factor XI* rs3756008 (A>T) in 200 Palestinian women

suffering from RPL as compared to 200 healthy women. Significant associations were only evident for *Factor V*: G1691A and H1299R polymorphisms.

RPL is a distressing social problem and is of particular concern to Palestinian families whose culture traditionally emphasizes the extended families. Despite extensive research to explain the causative effects of RPL, about 50% of RPLs are still idiopathic.

Hereditary thrombophilia is increasingly recognized as an important factor contributing to RPL. This inherited tendency of the body to inappropriate clot formation is influenced by the genetic make-up of the individual. Genetic variation, in terms of polymorphisms in the genes involved in the different aspects of the coagulation process, has been proposed as risk factors for RPL (Rull et al., 2012). Due to their important roles in the coagulation pathway, this study was conducted in order to investigate the association between genetic polymorphisms of *Factor V*: G1691A (R506Q; rs6025), H1299R (R2), Y1702C (rs118203907); *Factor II* G20210A (rs1799963), and *Factor XI* rs3756008 (A>T) and RPL among women experiencing RPL in the Gaza strip part of Palestine.

The study results showed that the allele frequencies of *Factor V* G1691A are significantly different between RPL patients and controls. The frequency of the polymorphic A allele was more prevalent in RPL patients (10.25%) than in controls (5.25%). It can be inferred that this polymorphism is associated with, and may increase the risk for RPL in our population. The A-allele seems to significantly double the risk for RPL (OR = 2.06).

Association between RPL and *Factor V* G1691A polymorphism observed in this study is in agreement with the findings reported by many other investigators (Wolf et al., 2003; Ulukufi et al., 2006; Motee et al., 2007; Torabi et al., 2009; Hussein et al., 2010; Gawish and Al-Khamees, 2013). In the contrary, other investigators found no relation between this polymorphism and RPL (Abd Allah and Hassan, 2014; Parand et al., 2013; Raziq et al., 2001). Interestingly, no G1691A polymorphism was detected in Japanese women with RPL or the controls (Kobashi et al., 2005).

The allele frequencies of *Factor V* A4070G were also significantly different between RPL patients and controls. The polymorphic G allele was more frequent in RPL patients (6.75%) than in controls (2.25%), and it can be concluded that this *Factor V* polymorphism is associated with RPL in our population and that the presence of the G-allele triples the RPL risk (OR = 3.14).

Investigations regarding the association of this polymorphism with RPL have also yielded variable results. Whereas, Torabi et al. (2012) in Iran found a significant association between *Factor V* A4070G and RPL risk, Sotiriadis et al. (2007) observed no difference in the prevalence of this polymorphism between RPL patients and controls.

When the three samples in which both G1691A and

Table 3. Genotype and allele frequencies of the investigated polymorphisms in RPL patients and controls.

Polymorphism	Genotype or allele	RPL (n = 200)	Controls (n=200)	P value	OR (95% CI)
<i>Factor V</i> G1691A	G/G	161(80.5%)	180 (90.0%)	0.01*	0.46 (0.26 to 0.82)
	G/A	37(18.5%)	19 (9.5%)	0.01*	2.16 (1.20 to 3.90)
	A/A	2 (1.0%)	1 (0.5%)	0.57	2.01 (0.18 to 22.35)
	Normal G	359 (89.75%)	379 (94.75%)		
	Minor A	41 (10.25%)	21 (5.25%)	0.009*	2.06 (1.19 to 3.56)
<i>Factor VA</i> 4070G	A/A	173 (86.5%)	191 (95.5%)	0.003*	0.302 (0.66 to 1.38)
	A/G	27 (13.5%)	9 (4.5%)	0.003*	3.31 (1.52 to 7.24)
	G/G	0 (0.0%)	0 (0.0%)	1.00	1.00 (0.19 to 50.65)
	Normal A	373 (93.25%)	391 (97.75%)		
	Minor G	27 (6.75%)	9 (2.25%)	0.003*	3.14(1.46 to 6.78)
<i>Factor VA</i> 5279G	A/A	196 (98.0%)	199 (99.5%)	0.21	0.25 (0.027 to 2.22)
	A/G	3(1.5%)	1 (0.5%)	0.34	3.03 (0.313 to 29.38)
	G/G	1 (0.5%)	0 (0.0%)	0.50	3.02 (0.122 to 74.46)
	NormalA	395 (98.75%)	399 (99.75%)		
	Minor G	5 (1.25%)	1 (0.25%)	0.14	0.19 (0.023 to 1.70)
<i>Factor II</i> G20210A	G/G	191(95.5%)	197 (98.5%)	0.09	0.32 (0.08 to 1.21)
	G/A	9(4.5%)	3 (1.5%)	0.09	3.09 (0.82 to 11.60)
	A/A	0 (0.0%)	0 (0.0%)	1.00	1.00 (0.02 to 50.65)
	NormalG	391 (97.75%)	397 (99.25%)		
	Minor A	9 (2.25%)	3 (0.75%)	0.097	3.05 (0.82 to 11.34)
<i>Factor XI</i> rs3756008 A> T	A/A	85 (42.5%)	103 (51.5%)	0.07	0.69 (0.46 to 0.03)
	A/T	114 (57.0%)	96 (48%)	0.07	1.44 (0.97 to 2.13)
	T/T	1 (0.5%)	1 (0.5%)	1.00	1.00 (0.06 to 16.09)
	Normal A	284(71.0%)	302 (75.5%)		
	Minor T	116 (29.0%)	98 (24.5%)	0.15	0.79 (0.58 to 1.09)

*P value \leq 0.05 is considered statistically significant.

A4070G polymorphisms coexisted were excluded, the A4070G minor allele remained as a significant risk factor for RPL with an odds ratio of 2.34 ($P = 0.0003$); indicating that the two polymorphisms independently affect the RPL risk.

In terms of alleles and genotype frequencies of *Factor V* A5279G polymorphism, no significant difference was observed between the RPL patients and controls. Therefore, this polymorphism seems to be unimportant in RPL patients in the investigated population.

Association studies of this single nucleotide polymorphism (SNP) with RPL also reported conflicting results. For instance, Torabi et al. (2012) showed that the minor allele of A5279G is associated with RPL whereas Coulam et al. (2006) indicated lack of difference between RPL and controls.

Regarding *Factor II* G20210A, our results showed that the differences in alleles and genotypes frequencies between RPL patients and controls did not reach

significance. The A allele was clearly more prevalent in RPL patients (2.25%) as compared to controls (0.75%). The low frequency of the minor A-allele of this polymorphism in our population may be the reason behind obscuring its association with RPL. Increasing the sample size further, may bring about different results. Still, lack of significant association between RPL and *Factor II* G20210A polymorphism observed in this study was in agreement with the findings reported by several investigators (Ardestani et al., 2013; Parand et al., 2013; Abu-Asab et al. 2011; Sotiriadis et al., 2007; Hohlagschwandtner et al., 2003). On the other hand, other reports showed significant association between this SNP and RPL risk (Gawish and Al-Khamees, 2013; Mierla et al., 2012; Torabi et al., 2012; Martinelliet al., 2000; Brenner et al., 1999).

The results for *Factor XI*: rs3756008 (A>T) polymorphism showed that there is no significant difference between the RPL patients and the controls in

terms of genotypes and alleles frequencies. It seems that this particular polymorphism does not contribute to the risk for RPL in our study sample.

Factor XI: rs3756008 (A>T) polymorphism was tested because it has been highlighted among the gene variants significantly associated with deep venous thrombosis (Bezemer et al., 2008). In terms of its association with pregnancy complications only one published report was encountered (Dahm et al., 2012) where they found no significant effect of this SNP on adverse pregnancy outcome. The same report however, showed that another SNP in *Factor XI* (rs2289252) is associated with pregnancy-related venous thrombosis.

Among all the investigated polymorphisms, *Factor XI* (rs3756008 A>T) is the only one whose genotypes frequencies significantly deviated from Hardy-Weinberg equilibrium (HWE). This significant departure from HWE could be due to a yet unidentified cause (e.g., an infectious agent) and deserves further investigation.

Controversial results are commonly encountered in association studies particularly, when conducted on different populations. This could be due to population and ethnic group variations in terms of type and frequency of alleles of polymorphic loci which in turn, influence the association outcome between risk alleles and multifactorial traits such as RPL. Another important difference between the various association studies is the sample size (power of the study) particularly when the minor allele of the variant locus is low in frequency. Small sample size would not reveal the significant association, even if present.

Screening women with RPL for hereditary thrombophilia is performed in a routine manner in many parts of the world. In order to be justified, we believe that screening for thrombophilia in RPL patients should be based on the results of association studies conducted on the same population. This guideline would also be cost-effective as it will define the number and type of the polymorphic alleles that should be tested.

Conclusion

The study showed that there is significant association between *Factor V*: G1691A (R506Q; rs6025) and H1299R (R2) polymorphisms and RPL. The authors recommend including the *Factor V*: A4070G (H1299R) in the thrombophilia workup of unexplained RPL cases in the study population.

Study limitations

Limitations of the study include low statistical power due to the modest sample size and the inability to adjust for the effects of gene-gene and gene-environment interactions on pregnancy.

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