J Assist Reprod Genet (2014) 31:1491–1496
DOI 10.1007/s10815-014-0294-0

GENETICS

Association of IL-17A and IL-17 F gene polymorphisms with recurrent pregnancy loss in Iranian women

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Received: 19 March 2014 / Accepted: 7 July 2014 / Published online: 17 September 2014

Abstract
Purpose Recurrent pregnancy loss (RPL) is defined as the occurrence of two or more miscarriages before the 20th week of pregnancy. T helper17 cells are a novel subset of T cells, which secrete IL (Interleukin)-17 and are known to be involved in inflammation, autoimmunity and rejection of non-self tissues. Herein, we studied the association between IL-17A rs2275913 and IL-17F rs763780 gene polymorphisms with RPL in Iranian women.
Methods A case-controlled study was performed on two groups consisting of 85 healthy women with at least one delivery and 85 women with the history of two or more RPLs. The frequency of IL-17A rs2275913 and IL-17 F rs763780 polymorphisms were determined by PCR-RFLP.
Results In the RPL group, the genotypes frequencies of rs2275913 polymorphism were GG (8.2 %), AG (30.6 %), and AA (61.2 %) and in the control group, were GG (3.5 %), AG (42.4 %) and AA (54.1 %). Statistical analysis showed no significant difference between the genotypes of AA, AG and GG in the two groups (p=0.1). The genotypes frequencies of rs763780 polymorphism were TT (43.5 %), TC (49.4 %) and CC (7.1 %) in the RPL group; whereas the frequencies were TT (25.9 %), TC (70.6 %) and CC (3.5 %) in the control group. Statistical analysis revealed a significant difference in the TT, TC, and CC genotypes frequencies between the case and the control groups (p=0.01).
Conclusions Our findings indicate that IL-17F polymorphism, rs763780, might be associated with a high risk of RPL in Iranian women.

Keywords IL-17 · Genotyping · Polymorphism · Recurrent pregnancy loss

Capsule The role of IL-17 in the pathogenesis of the recurrent pregnancy loss (RPL) has remained unclear. This is first report frequency of IL-17 gene polymorphism in RPL subjects and controls in Iranian population. IL-17 F polymorphism, rs763780, might be associated with a high risk of RPL.

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Introduction

Recurrent pregnancy loss (RPL) is defined as having had two or more miscarriages before the 20th week of pregnancy [1]. Different factors including genetic, anatomical, endocrine and infectious elements have been suggested to influence RPL process [2]. Various immunological abnormalities have been reported in women with RPL of unknown etiology including positive antiphospholipid antibodies, anti-nuclear antibodies, anti-thyroglobulin and anti-microsomal antibodies, elevated natural killer (NK) cell levels and NK cytotoxicity [3]. The role of some cytokines produced by peripheral blood mononuclear cells has also been investigated in women with a history of recurrent miscarriage [4].

T helper (Th) 17 cells are a novel subset of T cells which secrete IL (Interleukin)-17. Th17 cells are known to be involved in the pathogenesis of autoimmune, inflammation diseases and immunological rejection of non-self tissue. The retinoid orphan nuclear receptor (RORC) is a key regulator of

human Th17 cell lineage differentiation [5, 6]. Th17 cells produce IL-17, IL-22 and tumor necrosis factor alpha. The IL-17 family is composed of several closely-related cytokines including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17 F. The genes for two widely studied members of the family, IL-17A and IL-17 F, are located on chromosome 6P12. These two cytokines show high protein sequence similarity, bind to the same receptor and display similar biological activities [7, 8]. Binding IL-17 to its receptor initiates signalling pathways which induce the production of proinflammatory cytokines and chemokines and induce the recruitment of neutrophils [9, 10]. It has been shown that regulatory T (Treg) cells and Th17 cells play a role as regulator and effector cells in initiation and maintenance of pregnancy. Indeed, it has been demonstrated that an imbalance between regulatory and effector cells might lead to failure in implantation and other pregnancy problems. A study by Nakashima et al. showed that IL-17-positive T cells accumulated in the deciduas of women with RPL [11]. Wang et al. found that the proportion of Th17 cells in the peripheral blood and the decidua of women with inevitable abortion were significantly higher than women with normal pregnancy. The IL-17, IL-23 and RORC mRNA levels in decidual tissue form women with RPL have been reported to be higher compared with women with normal pregnancy. Moreover, there seems to be a reciprocal relationship between the number of Th17 cells and Treg cells in the peripheral blood and decidua [12]. Another study has shown that an increase in Th17 cells and decrease in Treg cells level in peripheral blood and decidua could lead to recurrent miscarriage [13]. Some studies have reported reduced numbers of Treg cells in the peripheral blood and decidua of women with unexplained recurrent spontaneous abortion [14, 15].

Some reports have pointed to the association between IL-17A and IL-17F polymorphisms with development and the clinical course of human disease. rs2275913, also known as G-197A, is a single nucleotide polymorphism (SNP) positioned in the upstream region of the IL-17A gene. It is located within a binding motif for the nuclear factor activated T cell (NFAT), a critical regulator of IL-17 expression. Therefore, it is conceivable that this SNP might influence the transcriptional regulation of IL-17 [16]. In a study, Espinoza et al. showed that the presence of allele G-197A is correlated with more efficient IL-17 secretion, likely due to the higher affinity of resulting sequence for NFAT [17]. IL-17F 7488 T/C (rs763780) is another polymorphism which is located within the coding region of IL-17 F and causes a His-to-Arg substitution at amino acid 161. It has been reported that the cytokine variant resulting from this substitution fails to induce proinflammatory cytokines and chemokines and antagonize the activity of wild type IL-17F [18].

Although the role of IL-17A and IL-17F cytokines in the pathogenesis of the RPL has remained unclear, we hypothesized that these cytokines could affect the survival of the embryo during pregnancy and that IL-17A and IL-17 F polymorphisms might influence RPL by altering the levels or the activity of gene product. To date, no studies have explored the potential association between IL-17A and IL-17F gene polymorphisms with RPL. In this study, we investigated for the first time the association between IL-17A (rs2275913) and IL-17F (rs763780) gene polymorphisms with RPL in Iranian women.

Materials and methods

Participants

This investigation was carried out as a case–control study on two different groups. Control group consisted of 85 healthy women of reproductive age with at least one delivery and no history of abortion. The case group consisted of 85 women with a history of two or more miscarriages and diagnosed as RPLs. The case samples included women referred to the Research and Clinical Center for Infertility in Yazd, Iran. All participants were primary RPL. Following tests and analyses were performed to exclude suspected etiologies of recurrent abortion: hysteroscopy or hystosalpingography, parental karyotyping, antiphospholipid antibodies (including anticardiolipin antibodies and lupus anticoagulant from IgM and IgG classes), anti–thyroid peroxidase and anti-thyroglobulin, TORCH syndrome, and hormonal disorders. Informed written consent was obtained from the enrolled patients and healthy subjects and information regarding age, number of abortions and number of pregnancy were collected. A sample of peripheral venous blood (2 ml) was taken and stored in an Ethylenediaminetetraacetic acid (EDTA)-coated tube at the time of enrolment. All of the experimental procedures were approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd.

Genetic analysis

The polymorphisms of rs2275913 and rs763780 in IL-17A and IL-17F were analyzed by the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) technique. DNA was extracted from whole blood samples with EDTA using AceuPrep Genomic DNA Extraction Bioneer Kit (Republic of Korea) according to manufacturer's instructions. Sequences containing the SNPs rs2275913 and rs763780 were located in Gen Bank, and primers were designed by PRIMER 3 software to amplify the appropriate DNA fragments. For SNP rs2275913, the following primers were used: forward 5'- TCT CCA TCT CCA TCA CCT TTG -3'and reverse 5'- GTC CAA ATC AGC AAG AGC ATC -3'. For SNP rs763780, the following primers were used: forward 5'- CAC TGG TGC TCT GAT GAG GA- 3'and reverse 5'- CAT TGT GCT TTG GCT TGC T- 3'.

Each PCR reaction was performed in a 25 μl tube containing 3 μl of DNA, 12.5 μl master mix (Ampliqon, Denmark), 7 μl distilled water and 1.25 μl of each of the reverse and forward primers. The PCR cycling conditions for IL-17A (rs2275913) consisted of an initial denaturation at 94 ° C for 5 min, followed by 30 cycles of denaturation for 1 min at 94 ° C, annealing for 1 min at 57 ° C and extension for 1 min at 72 ° C. A final extension was carried out for 5 min at 72 ° C (Applied Biosystems, ABI, Foster City, CA, USA). The PCR products were subjected to electrophoresis in a 2 % agarose gel stained with green viewer. Then, the PCR product size was digested by restriction enzyme, EcoNI according to kit instructions (Fermentas, CA).

The PCR cycling conditions for IL-17F (rs763780) consisted of an initial denaturation at 94 ° C for 5 min, followed by 30 cycles of denaturation for 1 min at 94 ° C, annealing for 1 min at 53 ° C and extension for 1 min at 72 ° C. Final extension was carried out for 5 min at 72 ° C. Following gel electrophoresis, the PCR product was digested by restriction enzyme, Nla III according to kit instructions (Fermentas, CA). All the gels were imaged using an E-gel imager (Life Technologies). About 10 % of the samples were randomly selected and the assays were repeated, and the results were 100 % consistent with the initial analyses.

Statistical analysis

Statistical analysis was performed with SPSS version 16 (SPSS Inc, Chicago, IL, USA). SNPs were evaluated for deviation from Hardy-Weinberg Equilibrium by chi-square test. The genotype and allele frequencies of SNPs rs2275913 and rs763780 were calculated by direct count. The differences in allele and genotypes frequencies between women with RPL and controls were determined using Fisher's exact test. The odd ratio (OR) and 95 % confidence intervals (CI) were calculated using logistic regression. P values<0.05 were considered statistically significant.

Results

The case and control groups were matched for age. Characteristics of the RPL and control group are shown in Table 1. All genotypes of the two polymorphisms were in Hardy-Weinberg Equilibrium. The undigested PCR product size was 815 bp for SNP rs2275913 (Fig. 1). Restriction digestion for the GG genotype generated 259, 270 and 286 bp fragments; whereas the AG genotype generated 259, 270, 286 and 529 bp and AA genotype produced 286 and 529 bp fragments. The undigested PCR product size was 635 bp for SNP rs763780 (Fig. 2). TT genotype produced 124,130 and 381 bp fragments; the TC genotype generated 124, 130, 381 and 511 bp fragments and CC genotype was characterized by 124 and 511 bp fragments.

Table 1 Characteristics of the RPL and control group

	RPL Group	Control Group
Age (yr) (Range)	30.84±5.2 (22 – 42)	29±4.4 (20 – 41)
No. of RPL (Range)	3±1.3 (2 – 7)	0
No. of Children (Range)	0	2.3±0.92 (2 – 5)

Data are presented as Mean±S.D RPL=recurrent pregnancy loss

The genotypes frequencies of polymorphism of rs763780 in the case group were TT (43.5 %), TC (49.4 %) and CC (7.1 %). The frequencies were TT (25.9 %), TC (70.6 %) and CC (3.5 %) in the control group. In the case group, the genotypes frequencies of polymorphism of rs2275913 were GG (8.2 %), AG (30.6 %), and AA (61.2 %) and in the control group, they were GG (3.5 %), AG (42.4 %) and AA (54.1 %).

The frequency of allele T of SNP rs763780 in the two groups was significantly different (p=0.01). The frequency of allele T was 68.2 % in the case group and 61.2 % in the control group. Besides, the frequency of allele C was 31.8 % in the case group and 38.8 % in the control group. The comparison between the case and the control group showed a significant difference in the three genotypes of TT, TC and CC (p=0.01) (odd ratio=1.363; 95 % CI :0.872 – 2.131). The results are shown in Table 2.

As the frequency of allele A was 76.5 % in the case group and 75.3 % in the control group, the difference in frequency of allele A in rs2275913 between the two groups was not significant (p=0.1). In the same way, the frequency of allele G was 23.5 % in the case group and 24.7 % in the control group, and again, there was no significant difference in the frequency of allele G (p=0.1). Also the comparison between the population of the case and the control groups in the three genotypes of AA, AG and GG revealed no significant difference (p=0.1) (Table 3).

Discussion

Early Th17 cell studies focused on inflammation, allograft rejection and autoimmune diseases such as inflammatory bowel diseases [19, 20]. In the past few years, a series of studies have explored the role of Th17 cells in the context of RPL. Th17 are a novel subset of $CD4^+$ T cells which can be effective on tolerance during pregnancy. Nakashima et al. investigated the proportion of Th17 levels in peripheral blood in the first, second and third trimester of pregnancy and found that the population of Th17 cells during pregnancy is constant [21]. Lee et al. reported an imbalance between Th1 and Th2 cells and suggested that increased numbers of Th17 cells and

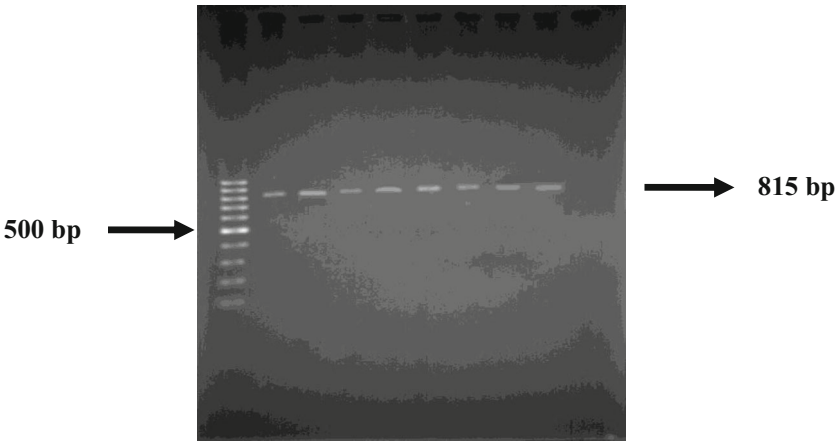

Fig. 1 Gel picture showing PCR product for SNP rs2275913

enhanced Th1/Treg ratio might lead to an inflammatory response which likely contributes to the development of RPL. They also showed increase numbers of IL-17-positive T cells in the peripheral blood of no pregnant women with a history of RPL. It is believed that these cells are actively involved in the pro-inflammatory immune responses at the maternal-fetal junction at the time of implantation which could subsequently lead to the development of RPL [22].

In the current study we investigated the potential relationship between IL-17 polymorphisms and susceptibility to RPL. To this end, we examined the association between IL-17A (rs2275913) and IL-17F (rs763780) gene polymorphisms with RPL. Our results showed a significant difference in genotypes frequencies of rs763780 polymorphism between case and control groups. The TC genotype in the case group (49.4 %) and the control group (70.6 %) showed the highest frequency. Interestingly, the frequency of allele T was significantly higher in the case group (68.2 %) compared with the control group (61.2 %). Genotypes frequencies for rs2275913 polymorphism did not show a significant difference between case and control groups and the AA genotype both the case group (54.1 %) and the control group (61.2 %) displayed the highest frequency.

The genotypes and allele frequency of rs2275913 IL-17A polymorphism and rs763780 IL-17F polymorphism have also been measured in some other disorders in different population. The results of various studies on this topic have been inconsistent.

Wang et al. Studied IL-7A and IL-7F polymorphisms in Chinese Han women with breast cancer. Their results showed that the rs763780 TT genotype frequency was 77.8 % in patient and 78.89 % in the healthy control group while the rs2275913 AG genotype frequency was 47.66 % in patients and 48.9 % in the control group. Also, they found an association between the SNPs in IL-17A but not IL-17F and breast cancer risk [23]. Association between IL-17 gene polymorphisms and risk of cervical cancer in Chinese women has been assessed by Quan et al. They found that the rs763780 TT genotype frequency was 71.4 % in patients and 77.1 % in control. The rs2275913 AG frequency was 45.7 % in women with cervical cancer and 46.4 % in healthy control. Moreover, there was a significant correlation between IL-17A rs2275913 and the risk for developing cervical cancer but no association between IL-17F rs763780 gene polymorphism and cervical cancer was observed [24]. Hayashi et al. investigated the association between gastro-duodenal disease and

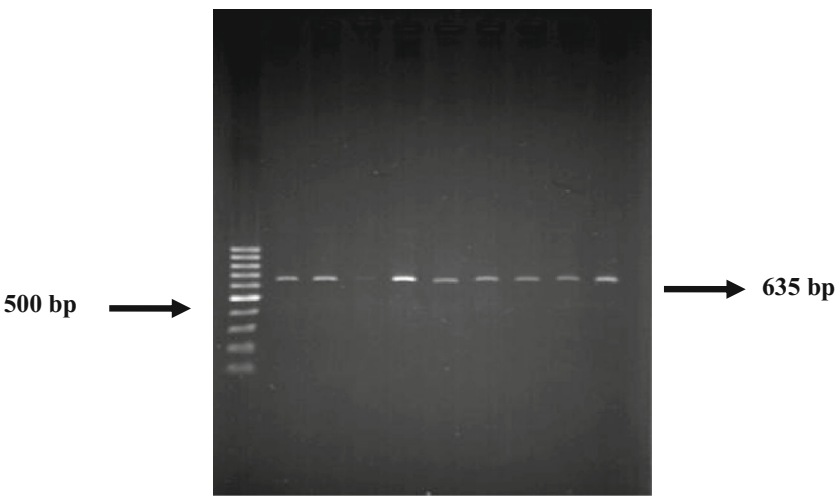

Fig. 2 Gel picture showing PCR product for SNP rs763780

Table 2 The frequencies of IL-17 F genotypes and alleles in RPL and control group

SNP	Allele frequency		Genotype frequency		
rs763780	T Allele	C Allele	TT	TC	CC
RPL group	116 (68.2)	54 (31.8)	37 (43.5)	42 (49.4)	6 (7.1)
Control group	104 (61.2)	66 (38.8)	22 (25.9)	60 (70.6)	3 (3.5)

Data are presented as No. (%). RPL=recurrent pregnancy loss P=0.01 OR=1.363; 95 % CI (0.872 – 2.131)

polymorphisms of rs763780 and rs2275913 in Japanese population. They reported that the TT genotype frequency of rs763780 was 78.9 % in control and 83.2 % in patients with gastro-duodenal ulcer and AG genotype frequency of rs2275913 was 52.4 % in control and 52.3 % in patients. Their findings indicated that rs2275913 influences the susceptibility to gastro-duodenal ulcer [25]. A study on Polish patients with rheumatoid arthritis showed that AA genotype frequency of rs763780 of IL-17 F was 88.6 % in patients and 92.5 % in healthy individuals without history of disease. The findings demonstrated that this SNP might be associated with increased disease activity in rheumatoid arthritis patients. Besides, the study showed that IL-17 gene polymorphisms were not associated with gender [26]. The difference in race might explain this discrepancy. The associations between SNPs of IL-17 and gastric carcinogenesis and ulcerative colitis have also been investigated [27, 28]. Moreover, Epinoza et al. have reported an association between rs2275913 genotype in the recipient side with the development of acute graft-versus-host disease following bone marrow transplants [29].

In the present study, we found that genotypes frequencies of rs763780 were significantly different in the RPL and control groups. Kawaguchi et al. examined the functional consequences of the H161R substitution using recombinant wild-type and mutant IL-17F proteins. They found that the expression and/or activity of IL-17F may be suppressed in IL-17 F/7488C allele carriers and that the IL-17F H161R variant blocked the induction of IL-8 expression by wild-type IL-17F [18]. Nonetheless, the level of serum IL-17F was not measured in the study so that IL-17F cytokine levels resulting from different genotypes could be compared . We found no significant association between IL-17A rs2275913 genotype frequencies and the risk of RPL. In literature, there is no any research to explain the association between this polymorphism and IL-17A production.

Table 3 The frequencies of IL-17A genotypes and alleles in RPL and control group

SNP	Allele frequency		Genotype frequency		
rs2275913	A Allele	G Allele	AA	AG	GG
RPL group	130 (76.5)	40 (23.5)	52 (61.2)	26 (30.6)	7 (8.2)
Control group	128 (75.3)	42 (24.7)	46 (54.1)	36 (42.4)	3 (3.5)

Data are presented as No. (%). RPL=recurrent pregnancy loss P=0.1

There are some potential limitations to our study which could affect the results. Our research is inherently limited by the study designed and we did obtain evidence for the role of rs763780 on the expression and activity of IL-17F. This is one of the limitations in our study. The size of sample may not be large enough which weakness our ability to solidity statistical association. In addition, only two SNPs were tested in subjects with RPL history and control. Further studies with a larger sample size in different population are needed to identify the association between IL-17F and IL-17A gene polymorphisms and RPL.

In summary, our findings indicate IL-17F polymorphism, rs763780, might be associated with a high risk of RPL in Iranian women. On the other hand we did not find any association between rs2275913 of IL-17A and the risk of RPL.

Acknowledgments Shahid Sadoughi University of Medical Sciences provided the grant for this research project. This manuscript is a part of in the M.Sc thesis of Soheil Najafi. The authors are grateful to Drs. Farshid Noorbakhsh and Kazem Barzegar for their critical reading of the manuscript and Dr. Hossein Fallahzadeh for statistical assistance.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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