Functional single nucleotide polymorphisms of matrix metalloproteinase 7 and 12 genes in idiopathic recurrent spontaneous abortion

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Abstract

Purpose The aim of this study was to investigate the potential association of *matrix metalloproteinase 7 (MMP7)* -181 A/G and *MMP12* -82 A/G functional single nucleotide polymorphisms (SNP) with idiopathic recurrent spontaneous abortion (IRSA) in Slovenian reproductive couples.

Methods A case–control study was conducted on 149 couples with 3 or more consecutive idiopathic spontaneous pregnancy losses and 149 women and men with at least 2 live births and no history of pregnancy complications. Genotyping of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs was performed using polymerase chain reaction and restriction fragment length polymorphism methods.

Results There were no statistically significant differences in the distribution of *MMP7* -181 A/G and *MMP12* -82 A/G genotype, allele, or haplotype frequencies between IRSA patients and controls, as well as patients' primary and secondary IRSA. We also found no association of *MMP7* -181 A/G and *MMP12* -82 A/G genotypes, alleles, and haplotypes with IRSA.

Conclusions We found no evidence to support the association between IRSA and *MMP7* -181 A/G and *MMP12* -82 A/G SNPs in Slovenian reproductive couples.

Capsule We found no evidence to support the association between IRSA and *MMP7* -181 A/G and *MMP12* -82 A/G SNPs in Slovenian reproductive couples.

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Keywords Single nucleotide polymorphisms · Pregnancy · Recurrent spontaneous abortion · Matrix metalloproteinases

Introduction

Idiopathic recurrent spontaneous abortion (IRSA) is defined as the spontaneous loss of three or more consecutive pregnancies [1]. This pregnancy complication, which occurs mostly during early gestation, is an intriguing phenomenon for clinicians and scientists due to the fact that the cause cannot be determined in 50–60% of couples [1–3].

Successful embryo implantation depends on a receptive endometrium and functional blastocyst, as well as a coordinated dialogue between them [4]. During the secretory phase, including the implantation window and decidual transformation, the expression profiles of endometrial genes are changed considerably compared to proliferative phase [5–8]. It has been suggested that abnormalities in gene expression during the secretory phase may lead to inappropriate endometrial development and, consequently, various reproductive disorders, including recurrent spontaneous abortion [9–12].

A key event in endometrial decidualization, trophoblast implantation, and placentation is the degradation and remodeling of the extracellular matrix (ECM), which is determined by a careful balance between matrix synthesis, modification, and degradation [13]. Matrix-degrading enzymes include a large family of matrix metalloproteinases (MMPs), which comprises 23 endopeptidases in humans [14].

During pregnancy, MMPs are secreted by both endometrial and trophoblast cells [15, 16]. Earlier studies have reported alterations in the expression of several MMP genes in women with IRSA and their spontaneously aborted conceptuses compared to women with normal pregnancies, which can lead to an altered ECM turnover [10, 12, 17–24]. In addition, we previously

evaluated the potential association of *MMP1*, 2, 3, and 9 functional single nucleotide polymorphisms (SNP) with IRSA and found a statistically significant increased frequency of the *MMP2* -735 CT and *MMP9* -1562 CC genotypes in IRSA women compared to controls, suggesting that these might be risk genotypes for IRSA [25]. In the present study, we extended this analysis to *MMP7* and *12* genes, both of which exert important functions in pregnancy, including implantation and remodeling of spiral arteries. Additionally, polymorphisms in these genes have been investigated in different disorders, including gynecological [26–28] and non-gynecological cancers [29–31], as well as reproductive disorders [32, 33] and various systemic disorders [34–36]. Our aim was to evaluate the potential association between IRSA in Slovenian reproductive couples and *MMP7* -181 A/G and *MMP12* -82 A/G functional SNPs, which are located in gene promoter regions.

Materials and methods

Subjects

A case–control study was performed to examine the potential association of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs with IRSA in Slovenian reproductive couples.

The study was approved by the Slovenian and Croatian National Ethics' Committees, and each participant provided written informed consent prior to entering the study. All participants were recruited through the Institute of Medical Genetics, Department of Obstetrics and Gynecology, University Medical Center, Ljubljana, Slovenia.

The IRSA group included 149 women and their 149 partners with a history of 3 or more consecutive miscarriages before the 22nd week of gestation, the etiology of which could not be explained by conventional criteria for RSA evaluation [1]. Exclusion criteria for RSA couples were chromosome aberrations in either partner, and, additionally in women, endocrine or metabolic disorders, autoimmune diseases or other systemic disorders, antiphospholipid syndrome, previous venous or arterial thrombosis, and uterine anatomic abnormalities. A total of 98 (65.8%) of couples had no live births (primary IRSA), whereas 51 (34.2%) had at least one live-born child (secondary IRSA). One hundred thirty-eight couples (92.6%) had at least 3 SAs, and 11 had 4 or more SAs (7.4%). In addition, 92% of couples had the SAs in the first trimester and 8% in the second trimester. Median age of IRSA women and men was 33 (range 23–46) and 34 (range 23–54), respectively.

The control group consisted of 149 unrelated healthy men and 149 unrelated healthy women with at least 2 normal term deliveries and no previous history of SA or any other reproductive disorder.

Molecular genetic methods

Genomic DNA of IRSA couples and control subjects was extracted from peripheral blood leukocytes by standard procedures using a commercially available kit (QIAGEN FlexiGene DNA kit, QIAGEN, Hilden, Germany). Extracted DNA was stored at -20°C .

Genotyping of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs was performed using the combination of polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) methods. Conditions were taken from previous studies and were slightly modified [26, 29] (Table 1). Polymerase chain reaction was carried in thermal cyclers (Mastercycle Personal, Eppendorf, Hamburg, Germany and 2720 Thermal Cycler, Applied Biosystems, Carlsbad, CA, USA). The PCR products and restriction fragments were visualized under ultraviolet light after electrophoresis on 1 and 3% agarose gels stained with GelRed (Olerup SSP, Saltsjobaden, Sweden), respectively. The presence of specific genotypes was determined by the band of expected size.

Statistical analysis

Statistical power was calculated using DSS Researcher's Toolkit (www.dssresearch.com/toolkit/spcalc/power_p2.asp). Hardy–Weinberg equilibrium was calculated using Simple Hardy–Weinberg Calculator—Court Lab (Washington State University College of Veterinary Medicine, Pullman, WA, USA). Haplotype frequencies were calculated using SNP analyzer Pro™ (version 1.8.581.342-2009-06-18, Istech Corp., CEO, Korea). Differences in genotype, allele, and haplotype frequencies between patients and controls were determined using chi-square test (Statistica for Windows, version 12, Statsoft, Inc., Tulsa, OK, USA). Associations of individual and combined *MMP7* -181 A/G and *MMP12* -82 A/G genotypes, alleles, and haplotypes with IRSA were estimated by calculating odds ratios (ORs) and their 95% confidence intervals (CIs) (Medcalc for Windows, version 14.12.0, Medcalc Software, Mariakerke, Belgium). *P* values ≤ 0.05 were considered statistically significant.

Results

The power of the present study was 98% to detect a 1.5-fold increase in the frequency of the *MMP7* -181G allele and 90% to detect a 2.0-fold increase in the frequency of the *MMP12* -82G alleles, respectively. Genotyping was unsuccessful in two men with IRSA, who were excluded from further analysis. The frequencies of *MMP7* -181 A/G and *MMP12* -82 A/G genotypes and alleles in IRSA and control groups, as well as primary and secondary IRSA, are shown in Tables 2 and 3. No statistically significant

Table 1 Conditions for genotyping of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs

Gene (chromosome locus)	SNP	Primers	PCR reaction conditions	PCR product	Restriction enzyme	Restriction products
<i>MMP7</i> (11q22.2)	-181 A/G (rs11568818)	5'-TGGTACCATA ATGTCCTGAATG-3'	94 °C (5 min)	150 bp	EcoRi ^a	
		5'-TCGTTATTGGCAG GAAGCACACAAT GAATT-3'	35×: 94 °C (30 s) / 47 °C (30 s) / 72 °C (30 s) 72 °C (5 min)			AA: 150 bp AG: 150 + 120 + 30 bp GG: 120 + 30 bp
<i>MMP12</i> (11q22.2)	-82 A/G (rs2276109)	5'-CTTCTAAACGGAT CAATCAG-3'	95 °C (5 min)	137 bp	PvuII ^a	AA: 137 bp
		5'-GTCAAGGGATGAT ATCAGCT-3'	35×: 94 °C (30 s) / 45 °C (30 s) / 72 °C (30 s) 72 °C (10 min)			AG: 137 + 119 + 18 bp GG: 119 + 18 bp

^a New England BioLabs, MA, USA

differences were found in the distribution of genotype and allele frequencies of either SNP between IRSA patients and controls or patients with primary and secondary IRSA. Genotype frequencies did not deviate from Hardy–Weinberg equilibrium in any of the study groups (data not shown). Furthermore, we found no association between the *MMP7* -181 A/G or *MMP12* -82 A/G SNPs and IRSA under dominant, recessive, and codominant genetic models (Table 4). In addition, the combined analysis showed no statistically significant differences in the frequencies of any *MMP7* -181 A/G and *MMP12* -82 A/G genotype combinations between IRSA patients and controls (data not shown). According to the Database of single nucleotide polymorphisms (dbSNP; <https://www.ncbi.nlm.nih.gov/snp>), allele and genotype frequencies obtained in our population are consistent with the European population for both polymorphisms.

Finally, we found no differences in the distribution of haplotype frequencies between IRSA and control groups, as well as primary and secondary IRSA (Tables 5 and 6).

Discussion

In this study, we investigated, for the first time, the potential association between *MMP7* -181 A/G and *MMP12* -82 A/G functional SNPs and IRSA in Slovenian reproductive couples.

Table 2 Genotype and allele frequencies of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs in IRSA and control women

	Patients (<i>N</i> = 149) <i>n</i> (%)	Controls (<i>N</i> = 149) <i>n</i> (%)	<i>χ</i> ²	<i>P</i> value	Primary IRSA (<i>N</i> = 98) <i>n</i> (%)	Secondary IRSA (<i>N</i> = 51) <i>n</i> (%)	<i>χ</i> ²	<i>P</i> value
<i>MMP7</i> -181 A/G								
Genotype								
AA	42 (28.2)	45 (30.2)	0.16	0.924	30 (30.6)	12 (23.5)	0.87	0.648
AG	84 (56.4)	81 (54.4)			53 (54.1)	31 (60.8)		
GG	23 (15.4)	23 (15.4)			15 (15.3)	8 (15.7)		
Allele								
A	168 (56.4)	171 (57.4)	0.06	0.804	113 (57.6)	55 (53.9)	0.38	0.538
G	130 (43.6)	127 (42.6)			83 (42.4)	47 (46.1)		
<i>MMP12</i> -82 A/G								
Genotype								
AA	116 (77.8)	114 (76.5)	4.07	0.130	75 (76.5)	41 (80.4)	0.29	0.590
AG	33 (22.2)	31 (20.8)			23 (23.5)	10 (19.6)		
GG	0 (0.0)	4 (2.7)			0 (0.0)	0 (0.0)		
Allele								
A	265 (88.9)	259 (86.9)	0.57	0.451	173 (88.3)	92 (90.2)	0.25	0.614
G	33 (11.1)	39 (13.1)			23 (11.7)	10 (9.8)		

Table 3 Genotype and allele frequencies of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs in IRSA and control men

	Patients (<i>N</i> = 147) <i>n</i> (%)	Controls (<i>N</i> = 149) <i>n</i> (%)	<i>χ</i> ²	<i>P</i> value	Primary IRSA (<i>N</i> = 97) <i>n</i> (%)	Secondary IRSA (<i>N</i> = 50) <i>n</i> (%)	<i>χ</i> ²	<i>P</i> value
<i>MMP7</i> -181 A/G								
Genotype								
AA	58 (39.5)	55 (36.9)	0.72	0.699	38 (39.2)	20 (40.0)	0.62	0.732
AG	64 (43.5)	63 (42.3)			44 (45.4)	20 (40.0)		
GG	25 (17.0)	31 (20.8)			15 (15.4)	10 (20.0)		
Allele								
A	180 (61.2)	173 (58.1)	0.62	0.432	120 (61.9)	60 (60.0)	0.10	0.757
G	114 (38.8)	125 (41.9)			74 (38.1)	40 (40.0)		
<i>MMP12</i> -82 A/G								
Genotype								
AA	114 (77.6)	113 (75.8)	0.12	0.728	72 (74.2)	42 (84.0)	1.81	0.178
AG	33 (22.4)	36 (24.2)			25 (25.8)	8 (16.0)		
GG	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)		
Allele								
A	261 (88.8)	262 (87.9)	0.11	0.746	169 (87.1)	92 (92.0)	1.58	0.209
G	33 (11.2)	36 (12.1)			25 (12.9)	8 (8.0)		

We found no significant differences in any of the allele, genotype, or haplotype frequencies between patient and control groups, or association with IRSA under any genetic model. Therefore, our results suggest that *MMP7* -181 A/G and *MMP12* -82 A/G functional SNPs are not associated with IRSA.

The investigated genes were selected based on their confirmed roles in human pregnancy, whereas the SNPs were

chosen according to their functionality and association with other disorders, including reproductive disorders.

Matrix metalloproteinase 7, also known as matrilysin or PUMP-1, has broad substrate specificity and is secreted mostly from the endometrial epithelium cells where attachment of the blastocyst occurs [37, 38]. In human placenta, MMP7 is secreted by cytotrophoblast and syncytiotrophoblast during early pregnancy; and by the third trimester only by

Table 4 Association of *MMP7* -181 A/G and *MMP12*-82 A/G SNPs with IRSA

		Women				Men			
		Patients vs. controls		Primary vs. secondary IRSA		Patients vs. controls		Primary vs. secondary IRSA	
Genetic model		OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
<i>MMP7</i> -181 A/G									
Dominant	AG + GG vs. AA	1.10 (0.67–1.82)	0.702	0.70 (0.32–1.52)	0.363	0.90 (0.56–1.44)	0.653	1.04 (0.52–2.08)	0.922
Recessive	GG vs. AA + AG	1.09 (0.58–2.04)	0.797	0.97 (0.38–2.47)	0.951	0.85 (0.47–1.53)	0.585	0.73 (0.30–1.77)	0.489
Codominant	GG vs. AA	1.07 (0.52–2.19)	0.850	0.75 (0.25–2.23)	0.604	0.77 (0.40–1.46)	0.414	0.79 (0.30–2.07)	0.631
Codominant	AG vs. AA	1.11 (0.66–1.87)	0.691	0.68 (0.31–1.53)	0.354	0.96 (0.58–1.60)	0.885	1.16 (0.54–2.47)	0.704
Codominant	AG vs. GG	1.04 (0.54–1.99)	0.913	0.91 (0.35–2.40)	0.851	1.26 (0.67–2.37)	0.474	1.47 (0.56–3.83)	0.434
Allele	G vs. A	1.04 (0.75–1.44)	0.804	0.86 (0.53–1.39)	0.538	0.95 (0.69–1.32)	0.773	0.93 (0.56–1.52)	0.757
<i>MMP12</i> -82 A/G									
Dominant	AG + GG vs. AA	0.93 (0.54–1.59)	0.782	1.26 (0.55–2.90)	0.591	0.91 (0.53–1.56)	0.728	1.82 (0.75–4.41)	0.182
Recessive	GG vs. AA + AG	0.11 (0.01–2.03)	0.137	0.52 (0.01–26.74)	0.747	1.01 (0.02–51.42)	0.995	0.52 (0.01–26.49)	0.743
Codominant	GG vs. AA	0.11 (0.01–2.05)	0.139	0.55 (0.01–28.21)	0.766	0.99 (0.02–50.39)	0.997	0.59 (0.01–30.09)	0.790
Codominant	AG vs. AA	1.05 (0.60–1.82)	0.873	1.26 (0.55–2.89)	0.591	0.91 (0.53–1.56)	0.728	1.82 (0.75–4.41)	0.182
Codominant	AG vs. GG	9.57 (0.50–185.08)	0.135	2.24 (0.04–120.61)	0.692	0.92 (0.02–47.57)	0.966	3.00 (0.06–163.16)	0.590
Allele	G vs. A	0.83 (0.50–1.36)	0.451	1.22 (0.56–2.68)	0.615	0.92 (0.56–1.52)	0.746	1.70 (0.74–3.92)	0.213

Table 5 Haplotype frequencies of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs and their association with IRSA in women

Haplotype	Patients (<i>N</i> =298) <i>n</i> (%)	Controls (<i>N</i> =298) <i>n</i> (%)	χ^2	<i>P</i> value	OR (95% CI)	<i>P</i> value	Primary IRSA (<i>N</i> =196) <i>n</i> (%)	Secondary IRSA (<i>N</i> =102) <i>n</i> (%)	χ^2	<i>P</i> value	OR (95% CI)	<i>P</i> value
<i>MMP7</i> -181												
<i>MMP12</i> -82			2.13	0.545					0.46	0.927		
A	147 (49.4)	142 (47.5)			1.07 (0.77–1.47)	0.682	98 (49.9)	50 (48.6)			1.04 (0.64–1.68)	0.872
G	118 (39.5)	117 (39.4)			1.04 (0.60–1.81)	0.887	75 (38.4)	42 (41.6)			0.88 (0.54–1.44)	0.625
A	20 (6.7)	29 (9.9)			0.64 (0.35–1.19)	0.162	15 (7.7)	6 (5.4)			1.33 (0.50–3.53)	0.572
G	13 (4.4)	10 (3.2)			1.33 (0.56–3.13)	0.516	8 (4.0)	4 (4.4)			1.04 (0.31–3.55)	0.947

Table 6 Haplotype frequencies of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs and their association with IRSA in men

Haplotype	Patients (<i>N</i> =294) <i>n</i> (%)	Controls (<i>N</i> =298) <i>n</i> (%)	χ^2	<i>P</i> value	OR (95% CI)	<i>P</i> value	Primary IRSA (<i>N</i> =194) <i>n</i> (%)	Secondary IRSA (<i>N</i> =100) <i>n</i> (%)	χ^2	<i>P</i> value	OR (95% CI)	<i>P</i> value
<i>MMP7</i> -181												
<i>MMP12</i> -82			1.24	0.742					1.35	0.718		
A	158 (53.7)	153 (51.3)			1.10 (0.80–1.52)	0.559	103 (52.8)	57 (57.1)			0.85 (0.52–1.39)	0.524
G	103 (35.1)	109 (36.6)			0.93 (0.67–1.31)	0.695	67 (34.4)	35 (34.7)			0.98 (0.59–1.62)	0.937
A	22 (7.5)	20 (6.8)			1.12 (0.60–2.11)	0.715	18 (9.4)	6 (6.1)			1.60 (0.61–4.17)	0.334
G	11 (3.7)	16 (5.3)			0.67 (0.31–1.48)	0.327	6 (3.3)	2 (2.1)			1.56 (0.31–7.89)	0.588

cytotrophoblast [39]. Consequently, it has been suggested that MMP7 is important in the implantation process [40, 41]. Furthermore, MMP7 degrades soluble vascular endothelial growth factor receptor 1 (sVEGFR1) and increases the bioavailability of VEGF₁₆₅, which promotes angiogenesis [42]. The G allele of the *MMP7* -181 A/G SNP creates a putative binding site for a heat shock transcription factor, thereby increasing *MMP7* gene promoter activity and transcription compared to the -181 A allele [34]. The G allele has been reported as a potential risk factor for several gynecological disorders, including endometriosis and adenomyosis [32], as well as endometrial [27], ovarian [26], and cervical cancers [28]. Moreover, the presence of the G allele has been associated with increased levels of malondialdehyde, a marker of lipid peroxidation, in severe preeclampsia [33]. Furthermore, the G allele has been associated with different types of extra-genital cancers [29, 30].

Matrix metalloproteinase 12 or macrophage elastase is also expressed by both the endometrium and trophoblast. Major sources of MMP12 are uterine natural killer cells and macrophages [43], interstitial and endovascular trophoblasts, as well as vascular smooth muscle cells [44]. The MMP12 is a key mediator of elastolysis and contributes to the remodeling of spiral arteries. Expression of the *MMP12* gene was found to be upregulated in deciduas of women with IRSA compared to controls [12]. The A allele of the *MMP12* -82 A/G SNP enhances the binding of the transcription factor activator protein 1, increasing promoter activity [45]. It has been suggested that the G allele is associated with epithelial ovarian carcinoma [46], whereas the AA genotype possibly contributes to a higher risk of disseminated colorectal carcinoma, chronic obstructive pulmonary disease, and systemic sclerosis [31, 35, 36].

The limitations of our study might be a relatively small sample size and the fact that genotyping was not performed on spontaneously aborted conceptuses. However, this study also has several strengths. For example, statistical power was sufficient and the selection criteria for patients and controls were strict. Moreover, considering that male genome has an inevitable role in reproductive success [47, 48], our study included male partners of IRSA women.

In conclusion, we found no evidence to support the association of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs with IRSA in Slovenian population. Additional research is needed on a larger group of IRSA couples and different populations to detect smaller differences in allele frequency between the two groups and establish the possible role of *MMP7* -181 A/G and *MMP12* -82 A/G SNPs in IRSA.

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Compliance with ethical standards

Ethical approval All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Written informed consent was obtained from all individual participants included in the study. The study was approved by Slovenian and Croatian National Ethics’ Committees and was performed in accordance with the ethical standards as described in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Studies with animals This article does not contain any studies with animals performed by any of the authors.

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