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Interleukin-1 Receptor Antagonist (IL-1RN) Gene Variable Number Tandem Repeats (VNTR) Polymorphism Association in men Infertility in Erbil City /Kurdistan Iraq

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Abstract:

The interleukin-1 family has multifaceted roles in men's reproductive syste. Out of these is interleukin-1 receptor antagonist (IL-1RN) which exists in men gonads, and in case of infection and inflammatory process, its activity is increased. The current study aims to verify a possible linkage of Variable Number Tandem Repeat (VNTR) polymorphism of the IL-1RN gene with human men infertility. The study groups enrolled included 100 infertile men and 100 fertile and healthy men. Their seminal fluids were subjected to analysis. Also peripheral blood samples were collected for the assessment or detection of polymorphic Variable Number Tandem Repeats (VNTR) polymorphism of interleukin-1 receptor antagonist gene (IL-1RN). Two alleles, namely IL-1RN1 allele corresponding to 410bp fragment and IL-11RN2 that corresponding to 240bp fragments, are a marker for human men infertility, detected by PCR technique. The results delineated a high frequency of IL-1RN2 allelic gene variants (26%), and two VNTR allelic gene variants carriers IL-1RN1 and IL-1RN2 (16%) among infertile men with significant impacts on sperm motility and morphology (P< 0.000-0.002) respectively. This prospective study in Kurdistan region (Erbil – Iraq) defined a significant impact of VNTR polymorphism of IL-1RN gene in the etiology of men infertility especially on sperm motility and morphology; particularly carriers of IL-1RN2 allelic variants.

Key word: IL-1RN1, IL-1RN2, Men infertility, Sperm motility and morphology, VNTR polymorphism of IL-1RN.

Introduction:

Infertility is worldwide problem that affects 15% of couples who need to conceive (1). The idiopathic causes of men infertility are multifactorial and may include genetic and epigenetic abnormalities (2,3,4). Leydig and Sertoli cells in the testis have an important role in the regulation of spermatogenesis. Cytokines are physiologically synthesized and have positive impacts on spermatogenesis (5,6,7,8) especially IL-1 and IL-6 (9). Members of IL-1 family including IL-1α, IL-1β, and IL-1RN (IL-1 receptors antagonist), are pleiotropic cytokines that participate in inflammatory, immune-regulation, homeostatic function (10), and possibly at risk of a single nucleotide gene polymorphism (11,12,13).

In men gonads, cytokines especially 1L-1 and 1L-6 have positive impact on spermatogenesis and the development of functional spermatozoa (14,15,16) but with the risk of IL-1α.IL-β and IL-1RA gene polymorphism. Such a positive impact on spermatogenesis might have negative impacts, especially decreasing of sperm motility (17).

In the early 1990s, the functional role of Variable Number Tandem Repeats (VNTRs) in the second intron of the IL-1RN gene was confirmed (14). VNTRs are minisatellites with core sequences not less than 10-20 nucleotides and vary in number from several to several tens (18,19). Recently, studies have referred to the involvement of VNTRs in predisposition to a broad spectrum of

pathological conditions. Especially (IL-1RA) gene (IL‑1RN) located in intron 2 (rs2234663) is associated with cutaneous melanoma (20), Vitiligo (21), Non-atopic bronchial asthma (22). VNTRs can be localized in both coding and non-coding regions of genes such as in introns, in promoter sequences, and 5 UTR and 3 UTR, therefore, their location can determine several differences in the transcriptional level and function of expressed molecules (23). Some genes where the VNTR that is located within the gene sequence or near the gene has an impact on the level of gene expression (24). The variable number tandem repeating (VNTR) polymorphism has been reported within intron 2 of the human IL1RN (25). Five allelic variants (I, II, III, IV,V) are detected for VNTR of IL-1RN gene,with alleles I and II being the most frequent in the general population whereas the frequencies for VNTR alleles III, IV, and V do not exceed 5% (19,26).

VNTR of the IL-1RN gene has five allelic variants (23). The most frequent alleles belong to 1and 2, whereas the frequencies of the others do not exceed 5% (27). The level of expression of alleles 1 and 2 of the IL-1RN gene are associated with the production of IL-1RN protein with different levels and distinctive unique intracellular signaling pathway (28,29).

The impacts and association of VNTR polymorphism of IL-1RN with pathological conditions became pronounced after discovering its fundamental and functional role in several genes such as genes of insulin (30,31), dopamine transporter (15), serotonin transporter (32), endothelial nitric oxidase synthase (26) and interleukin 1 receptor antagonist (IL1RN) (17, 33) as VNTRs are localized either within the gene sequences or near the gene that affects the level of gene expression (23). Accordingly, polymorphism of IL-1RN2 VNTR supports the genetic susceptibility to human men infertility (27).

The cornerstone of this prospective study is to define the possible role of VNTR polymorphism of the human IL-1RN gene in the etiology of men infertility, in addition to studying the correlation of carrier of IL-1RN allelic gene variants with seminal fluid parameters, namely motility and morphology.

Material and Methods:

The study is a case-control one which included 100 infertile men, and 100 healthy individuals (men without any history of infertility problems or genital tract diseases) with the same ethnicity. They were enrolled over the period from February to September 2018. The seminal fluid analysis was carried out at the laboratory Department of Rizgary Teaching Hospital [Erbil-IRAQ]. The data were collected by interviewing the study groups through a structural questionnaire regarding men infertility. Patients have been married for a minimum of one year, and those having unprotected intercourse were especially considered for this study. Exclusion criteria were: patients with hypogonadism, obstructive azoospermia, chronic diseases, history of pelvic /spinal injuries, and karyotype abnormalities. The consent was obtained verbally from all patients, and the study was approved by the ethics committees of the Medical Research Center/Hawler Medical University. Assessing the seminal fluid for the study groups was performed after 3-5 days of sexual abstinence according to the guideline of the World Health Organization (WHO) to ascertain their infertility status and to evaluate the quality and quantity of sperm. Seminal fluid was investigated for the macroscopical (appearance, volume, PH, viscosity, gelatinous) and microscopical (sperm count, sperm motility, sperm morphology) analysis.

Detection of IL-1RN VNTR Gene Polymorphism

Whole blood was taken from the study groups and collected in EDTA tube (2.5 ml) then kept at - 20c°. Detection of VNTR of the *IL-1R*N gene polymorphism from the collected blood samples was assessed by using the polymerase chain reaction technique carried out at the Medical Research Center/Hawler Medical University in Erbil City/ IRAQ. Briefly, DNA was isolated from the blood samples (100 prep Fermentas DNA extraction kit**),** and the polymorphic region was amplified by PCR (Bioron / Genekam Biotechnology ready to use PCR master mix). The extracted DNAs were subjected to thirty cycles, (the protocol followed for PCR was initiation denaturation for five minutes at 94˚C followed by 30 cycles of denaturation for 40 second at 94˚C, then annealing for 40 second at at 56˚ C, followed by an extention for 40 second at 72˚C and a final extention at 72˚Cfor five minutes after 30 cycles). The amplification of IL-1RN VNTR Gene Polymorphism was done with forward primes 5-CTCAGCAACACTCCTAT-3 and reverse primer 5-TCCTGGTCTGCAGGTAA-3. The PCR products were analyzed by 2 % agarose gel electrophoresis for 55 minutes at 97 V. (Genekam Biotechnology AG, Germany). The samples were scored as positive for IL-1RN1 VNTR allele corresponding to a 410-bp fragment and 240 bp fragment corresponding to IL-1RN2 VNTR allele.

Statistical Analysis

The statistical analysis was performed by SPSS software version 19. Qualitative parameters

were compared between groups by Pearson Chi-square, while quantitative variables were expressed as the mean standard deviation (SD). Differences were considered statistically significant at $p \leq 0.05$.

Results:

The demographic characteristics of the 200 fertile and infertile men are shown in (Table 1). No significant differences were found between subjects regarding age, BMI and duration of the marriage ($p>0.05$). The infertile group included 100 infertile men, among them 36 subjects were smokers, three subjects were alcohol drinkers, and 19 subjects were heavy smokers. Regarding semen quality, especially immotile sperm, and abnormal morphology, a highly significant change among infertile men, was defined as compared with fertile men ($p=0.000$) (Table 1).

Table 1. Demographic characteristics and seminal analysis of fertile and infertile men

		Fertile men No (100) (Mean±SD)	Infertile men No(100) (Mean±SD)	p. value
Age		33.35±6.29	32.01±6.45	0.13^{NS}
BMI		25.79±3.39	26.87±5.52	0.1^{NS}
Duration of marriage		6.51±5.45	7.81±8.29	0.19^{NS}
Smoking	Yes	0	36	0.000^{S}
	No	100	64	
Alcohol consumption	Yes	0	3	0.081^{NS}
	No	100	97	
Hookah	Yes	0	19	0.000^{S}
	No	100	81	
Men with gene polymorphism	Yes	1	42	0.000^{S}
	No	99	58	
Seminal fluid analysis				
Volume (ml)		3.12±0.61	2.86±1.33	0.073^{NS}
Concentration (10^6 / ml)		70.94±18.55	51.86±38.74	0.000^{S}
Total count (10^6 /ejaculate)		218.01±67.59	144.7±124.77	0.000^{S}
Motility	Motile	71.5±13.57	49.1±23.24	0.000^{S}
	Immotile	27.85±14.31	50.9±23.24	0.000^{S}
Morphology	Normal	68.25±4.99	37.2±19.13	0.000^{S}
	Abnormal	31.75±4.99	62.8±19.13	0.000^{S}

NS: non-significant, S: significant

The frequencies for IL1RA VNTR gene polymorphism and their association with semen quality were compared between infertile men with and without gene polymorphism (Table 2). Thus infertile men with gene polymorphism showed a significant increase in immotile sperm and abnormal morphology ($p=0.000$ and 0.047), respectively.

Table 2. Seminal fluid analysis of infertile men in association with IL-1RN VNTR gene polymorphism.

		Infertile men without gene polymorphism No (58) (Mean±SD)	Infertile men with gene Polymorphism No (42) (Mean±SD)	p. value
Volume (ml)		2.67±1.32	3.12±1.32	0.094^{NS}
Concentration (10^6 / ml)		45.83±33.87	60.19±43.67	0.067^{NS}
Total count (10^6 /ejaculate)		122.91±111.57	174.77±136.71	0.04^{S}
Motility	Motile	59.22±24.92	35.12±9.78	0.000^{S}
	Immotile	40.78±24.92	64.88±9.78	0.000^{S}
Morphology	Normal	40.43±22.87	32.74±10.99	0.047^{S}
	Abnormal	59.57±22.87	67.26±19.99	0.047^{S}

NS: non-significant, S: significant

two allelic IL-1RN VNTR carrier on sperm motility and morphology. Table (3) refers to the seminal fluid analysis found in relation to single IL-1RN VNTR variant allele or two allelic gene variants.

In infertile men, allelic frequencies were 26 percentage for IL-1RN2 allele and 16 percentage for two allelic variants namely IL-1RN1 and IL-1RN2 (Table 3), with highly significant impacts of

Table 3. seminal fluid finding according to single or two IL-1RN ,VNTR allelic genes variant.

		Infertile men with single allelic gene variant/IL-1RN2 allele N (26) (Mean±SD)	Infertile men with two allelic gene variants /IL-1RN1 and IL-1RN2 N (16) (Mean±SD)	p. value
Volume (ml)		3.48±1.28	2.53±1.19	0.022 S
Concentration (10^6 / ml)		54.73±36.95	69.06±52.92	0.307 NS
Total count (10^6 /ejaculate)		189.73±142.8	150.47±126.79	0.373 NS
Motility	Motile	39.04±8.49	28.75±8.47	0.000 S
	Immotile	60.96±8.49	71.25±8.47	0.000 S
Morphology	Normal	36.73±7.48	26.25±12.85	0.002 S
	Abnormal	63.27±7.48	73.75±12.85	0.002 S

NS: non-significant, S: significant

Among the fertile men,only one subject harbor IL-1RN2 is allelic variant. Infertile men thus with IL-1RN VNTR gene polymorphism had a significant decrease in semen quality compared with infertile men without gene polymorphism. Significant correlation was found between IL-1RN VNTR gene polymorphism and sperm motility (r=0.517; p=0.000) and with abnormal morphology (r=0.468; p=0.002) (Table 4).

Table 4. Correlation between carriers of IL-1RN2 allelic variant and sperm motility and morphology

Gene polymorphism	Sperm Motility		Sperm Morphology	
	Motile	Immotile	Normal morphology	Abnormal morphology
Pearson correlation	- 0.517	0.517	- 0.468	0.468
Significane (2-tail)	0.000	0.000	0.002	0.002

According to Fig. 1 (PCR gel electrophoresis), the samples were scored as positive for IL-1RN1 allele that corresponds to a 410-bp fragment (4 copy of the 86bp), and as IL-1RN2 allele that corresponds to 240-bp fragment (2 copy of the 86bp). Samples 1,2 contains two allelic gene variants (IL-1RN1 and IL-1RN2) that correspond to 410 bp fragment and 240bp fragment. Sample 3 does not have this type of gene, wheres samples (4,5,7) were with single allelic gene variant/IL-1RN1 allele that corresponds to a 410-bp fragment. Sample 8 contains single allelic gene variant/IL-1RN2 allele that corresponds to a 240-bp fragment, and sample 15 contains gene which has 410 bp other band above this band which may belong to artifact band.

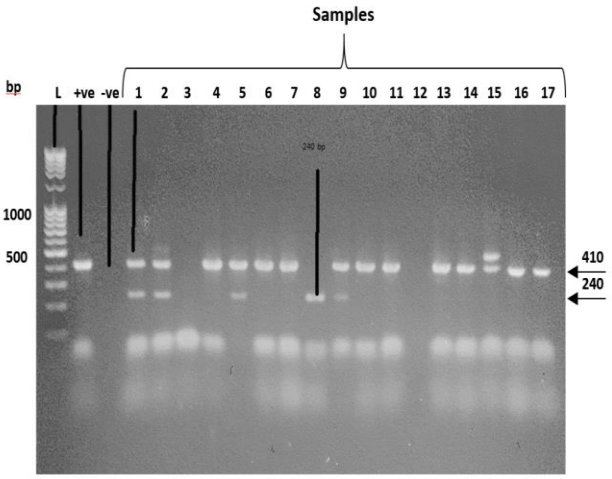

Figure 1. PCR amplification of the polymorphism gene of infertility men (2 % agarose for 55 minutes at 97 V.) Lane 1 is the 100 bp Marker, lane 2 is a positive control, and lane 3 is a negative control. The remaining lanes are the samples used in this study.

Discussion:

A unique feature of members of the IL-1 system is the naturally occurring IL-1RN (10) that maintains homeostatic regulation of IL-1 cytokine.

The results of the present study revealed a unique prevalence of IL-1RN2 allelic variant carriers in 26% of infertile men, with 16% of infertile men with two allelic gene variant carriers, IL-1RN1 and IL-1RN2, with significant impact and correlation of VNTR gene polymorphism with sperm motility and morphology. Our finding agrees with the first study published in 2012 that clarified the risky linkage of the carrier of IL-IRN2 variant allele with human men infertility (27). However, it disagrees with the second worldwide study published by Zamani-Badi *et al*, who refers to a non-significant association between IL-1RN VNTR and men infertility (17); however, subgroup analysis showed that men with VNTR genotype were associated with increased susceptibility to infertility in azoospermia (34).

Seminal fluid analysis of infertile men according to the number of VNTR allelic variants of the IL-1RN gene showed a highly significant impact of two allelic gene variants than a single variant regarding sperm motility (p=0.000) and morphology (p=0.002). In the present study, around 60% of sperm were immotile in infertile men with single IL-1RN2 VNTR gene polymorphism; whereas more than 70% of sperm were immotile among infertile men with two IL-1RN VNTR allelic variant. The linkage between –alleles I and II of IL-1RA gene and men infertility is related to the differences in the level of IL- 1RA protein synthesis and distinctions in the intracellular signaling pathways. Particularly, carriers of allele II of IL-1RA had a higher level of IL-1RA protein that non-carrier peoples (35). Besides, carriers of particularly IL-1RA II VNTR allelic variant had higher level of serum leptin and body fat masses (36). According to expression of a higher level of IL-1RA, protein of the men carrier of allele II of IL-1RA had a harmful: impact on IL-1. IL-1 is essential during spermatogenesis and the development of functional spermatozoon (16,37).

The expression level of IL-1RN protein is tissue-specific depending on the VNTR alleles (23). Thus as VNTR is defined as minisatellite, alleles I and II of L-1RN gene are associated with the expression of IL-1RN protein of different levels that lead to distinctive intracellular signaling pathway (29).

This prospective study might be the 3rd worldwide approach assessed in Kurdistan region (Erbil-Iraq) after two studies, one in Indian (18) and the other in Iran (17). The present study delineates a significant impact of alleles I and II of VNTR, IL-1RA gene variant on sperm motility and morphology in comparison with infertile men without allelic IL-1RN gene variant in our local community which agrees with Indian study (18) and disagrees with Iranian study (17).

Conclusion:

In summary, we concluded that the VNTR polymorphism of IL-1RN gene had an imporatant role in the etiology of men infertility particularly on sperm motility and morphology.

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Ethical Statement

Ethical standards in this research were rendered and approved by an expert committee in the Medical Research Center/Hawler Medical University. The committee collectively convened to assess this research, and they accepted it as NO 1-1-96 study on March 18, 2018. The letter is attached to the supplementary materials' paper. Furthermore, the ethical conducts were under the accordance of with the "Declaration of Helsinki". The selections of seminal fluid were derived and analyzed in Rizgari Teaching Hospital. Strictly considering the guidelines of the world Health Organization (WHO), the participants displayed consent and commitment to the study. Moreover, based on the mentioned organization's **st**andards, the patients refrained from sexual activities for 3-5 days. regarding gene polymorphism, whole blood was taken from the participants; and the gene detection was carried out in the medical Research Center/Hawler Medical University.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee in Hawler Medical University.

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تعدد الأشكال المترادفة المتعاقبة لمورث مضاد مستقبل الحريك الخلوي-1 و علاقته بالعقم عند الرجال في أربيل/كوردستان العراق

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الخلاصة:

عائلة الحريك الخلوي -1 لها أدوار متعددة في الجهاز التناسلي الذكري، ومن بينها مضادات مستقبلات الحريك الخلوي -1 (IL-1RN) الموجودة في الغدد التناسلية الذكرية، حيث تزداد نشاطها عند الاصابات بالعدوى والالتهاب. تهدف الدراسة الحالية إلى التحقق من وجود صلة محتملة لتعدد الأشكال المترادفة المترادفة (VNTR) للجين IL-1RN مع العقم عند الذكور. شملت مجموعات الدراسة المسجلين 100 من الرجال المصابين بالعقم و 100 من الرجال الأصحاء. حيث تم تحليل السوائل المنوية للمجموعات المشاركة. تم جمع عينات الدم المحيطي لتقييم أو الكشف عن تعدد الأشكال المترادفة المترادفة (VNTR) لجين مضادات مستقبلات الحريك الخلوي -1 (IL-1RN) لنمطين من الاليلات وهما أليل IL-1RN1 يتوافق مع 410 زوج قاعدي و IL-11RN2 يتوافق مع 240 زوج قاعدي كعلامة على العقم عند الذكور، باستخدام تقنية PCR حددت النتائج ارتفاع وتيرة التغاير الاليلي IL-1RN2 (26٪) ، واثنين من التغاير الاليلي VNTR ناقلات IL-1RN1 و IL-1RN2 (16٪) من الرجال المصابين بالعقم مع تأثيرات كبيرة على حركة الحيوانات المنوية واشكالها (P<0.000-0.002) على التوالي. هذه الدراسة التى تم تقييمها في إقليم كردستان (أربيل – العراق) والتى حددت تأثيراً كبيراً لتعدد الأشكال المترادفة المتعاقبة VNTR لجين IL-1RN في مسببات العقم عند الذكور خاصة على حركية الحيوانات المنوية واشكالها، ولا سيما ناقلات أليلية البديل IL-1RN2.

الكلمات المفتاحية: مضادات مستقبلات الحريك الخلوي – N1 الاولى (IL-1RN1)، مضادات مستقبلات الحريك الخلوي – N1 الثانية (IL-1RN2)، العقم عند الذكور، حركة وشكل الحيوانات المنوية, تعدد الأشكال المتعاقبة المترادفة (VNTR) لمضادات مستقبلات الحريك الخلوي -1 (IL-1RN)،.