Original Article J Korean Orthop Assoc 2010; 45: 379-385 • doi:10.4055/jkoa.2010.45.5.379 www.jkoa.org

Association of *GnRH1* Polymorphisms with Rheumatoid Arthritis in a Korean Female

한국인 여성 류마티스성 관절염 환자에서 *GnRH1* 다형성 유전자 발현의 연관성

Yu Mi Kim, M.D., Ph.D.[†,‡], Kye Young Han, M.D.*, Ph.D., Eun Bi Kwak[†], Wanjoo Chun, Ph.D.[†], Sung Soo Kim, M.D., Ph.D.[†], and Hee Jae Lee, Ph.D.[†]

*Departments of *Orthopedic Surgery, [†]Pharmacology, School of Medicine, Kangwon National University, Chuncheon, [‡]Department of Orthopedic Surgery, Sanbon Hospital, Wonkwang University, Gunpo, Korea*

Purpose: Rheumatoid arthritis (RA) is a common, chronic inflammatory arthritis that develops most often in women. Gonadal hormones may account for the sexual dimorphism in the immune response and for the greater incidence of autoimmune disease in females. Gonadotrophin- releasing hormone (GnRH), one of the gonadal hormones, plays an important role in immune system modulation. This study examined the effects of single nucleotide polymorphisms (SNP) in GnRH on gender differences in the pathophysiology of RA.

Materials and Methods: The presence of SNPs rs2659590, rs2321248, rs6186, rs6185, and rs2321049 in the human GnRH1 gene was confirmed in Korean RA patients by Taqman® SNP genotyping assays. A total of 153 unrelated female, Korean RA patients and 96 female Korean controls participated.

Results: There were no significant associations between GnRH1 polymorphisms and RA. However, we found that the rs2659590, rs6185 and rs2321248 polymorphism might be associated with a susceptibility to aberrantly high erythrocyte sedimentation rates in female RA patients.

Conclusion: Additional studies, with a larger number of patients and in different populations will be required to assess whether GnRH1 polymorphisms and these haplotypes could be used as susceptibility or resistance markers in RA. To our knowledge, this study is the first to analyze associations between SNPs of GnRH1 and RA.

Key words: gonadotrophin-releasing hormone 1, rheumatoid arthritis, single nucleotide polymorphism, association study

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease associated with swelling and pain in multiple joints.[1] Despite intensive research, the cause of RA remains obscure. Proposals of the initiating event include an infectious agent or other environmental exposure but genetic, hormonal, and reproductive factors may all contribute to developing RA. RA affects 1% to 2% of adults and, like most autoimmune diseases, develops most often in women, with a female/male ratio of 3:1.[2] Previous report reviewed that hormonal involvement is the higher incidence in female RA patients, because disease symptoms lessen during pregnancy and exacerbate in the postpartal period.[3] Evidence for endocrine involvement in RA tissue and cells include presence of androgen and estrogen receptors, high concentrations of biologically active steroids, key enzymes of steroid metabolism, and significant changes of estrogen to androgen ratio. These data suggest that individual immune cells, including synovial macrophages, may behave as steroid-sensitive cells.[4] Previous studies showed that

Received December 30, 2009 **Accepted** July 1, 2010
Correspondence to: Hee Jae Lee, Ph.D.
Department of Pharmacology, School of Medicine, Kangwon National University, Hyoja-dong, Chuncheon 200-701, Korea
TEL: +82-33-250-8850, **FAX:** +82-33-255-8809
E-mail: heejaelee@kangwon.ac.kr

*This work is supported by Clinical Medicine Research Grant (2007) funded by Kangwon National University Hospital.

the immunomodulatory effects of androgens and estrogens may be mediated indirectly.[5] One of the best-characterized targets for feedback actions of gonadal steroids is the hypothalamic hormone gonadotrophin-releasing hormone (GnRH).

GnRH is a peptide synthesized and released by the hypothalamus that is responsible for the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. GnRH1 gene located on chromosome 8 p21-11.2 synthesizes precursor GnRH1 protein of 92 amino acids, which is processed to GnRH1 decapeptide in mammals.[6] The gonadotroph cells in the anterior pituitary are bathed with pulsatile GnRH which then stimulates its own receptor (GnRHR) to cause secretion of LH and FSH. In females, the acute rise of LH during the LH surge, brought about by the process of GnRH-self priming, triggers ovulation.[7] GnRH itself has been shown to be immunostimulatory. Immune cells produce bioactive GnRH and express receptors for GnRH.[8-11] Previous studies showed that GnRH exerts stimulatory influences on expression of the interleukin-2 receptor, on B and T lymphocyte proliferation, and on serum IgG levels.[12,13] Based on those data, it was hypothesized that differences in responsiveness to GnRH might be due to gender differences in expression of GnRH receptor or due to gender differences in expression of G proteins.[13]

We examined five single nucleotide polymorphisms and haplotypes in the *GnRH1* regions and their association with susceptibility and severity with RA in female Korean patients.

Materials and Methods

1. Subjects

A total of 153 unrelated Korean female RA patients were participated (Table 1). Each patient was diagnosed by a rheumatologist and diagnosed according to diagnostic criteria, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and bone erosion. The control subjects (96 female) were recruited after they had been designated as no clinical evidence of RA in a general health check-up program. Written informed consent was obtained from all subjects. This study was approved by the Ethics Committee of Kyung Hee University, Faculty of Medicine.

2. Genotyping

Genomic DNA was extracted from whole blood cells using a NucleoSpin® Blood kit (Macherey-Nagel, Easton, PA, USA). Five polymorphisms of a GnRH1 gene were selected (Fig. 1). Of the 5 SNPs known to be exist in GnRH1 (http://www.ensembl.org; www.ncbi.nlm.nih.gov/SNP), two SNPs (rs6186, rs6185) were existed in coding region. The corresponding probes were ordered at the company Applied Biosystems, https://products.appliedbiosystems.com (Table 2). Allelic discrimination using fluorogenic probes (5' nuclease assay, Taqman®) was chosen for genotyping on the ABI PRISM 7700 Sequence Detection Systems (Applied Biosystems, Foster City, CA, USA) and consisted of the use of allele-specific fluorogenic probes.[14] Twenty nanograms of DNA were amplified by

Table 1. List of Selected SNPs and Context Sequence of Taqman® Probe in GnRH1 Gene

SNP No.	Function	Assay ID*	Context Sequence ([VIC/FAM])
rs2659590	3' near	C__26104141_10	GGAAATCTGATGCTTCACACAGGAT[A/G]TGTAAGTTAAGTGGGTGTGTTGCTT
rs2321248	Intron	C__15761941_10	TGCGCCACTGCACTCCAAAAAAAAC[A/G]AAAAAGGAAATAACGACGTCTGCCC
rs6186	Exon (Phe61Phe)	C__12105199_10	AACGTGGCTGGTGCGTGGTGCATTC[A/G]AAGCGTTGGGTTTCTGCCAGTTGAC
rs6185	Exon (Trp16Ser)	C___1529427_1_	CTGGCTGGAGCAGCCTTCCACGCAC[C/G]AAGTCAGTAGAATAAGGCCAGCTAG
rs2321049	Promoter	C___1529429_10	AACCCCCGGCATTTAGTGAGCATTC[A/G]GTAAGTATAGGTTTGAATGAATGAA

*TaqMan® SNP Genotyping Assays: https://products.appliedbiosystems.com/ab/en/US/adirect/ab?cmd=ABGTKeywordSearch.

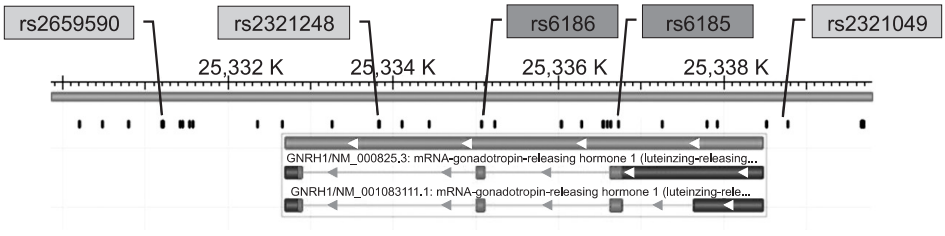

Figure 1. Schematic of the gonadotrophin-releasing hormone (GnRH1) gene. Shown are the 3 exons and 2 introns of the GnRH1 gene and the approximate location of each polymorphism identified in the present study.

AmpliTaq Gold DNA polymerase which was included in Taqman® Universal Master Mix (Applied Biosystems). The PCR reactions were as follows: one step of 10 min at 95°C followed by 40 cycles of two-step PCR with denaturation at 92°C for 15 s and annealing and extension at 60°C for 1 min. Five percent of all samples were genotyped again for quality control.

3. Statistics

For theses association study, Hardy-Weinberg equilibrium (HWE) for all SNPs was assessed using SNPstats (http://bioinfo.iconcologia.net/index.php).[15] A linkage disequilibrium (LD) block of polymorphisms was tested using Haploview (version 4.0).[16] The haplotypes and their frequencies were calculated by the EM algorithm.[17] Multiple logistic regression models were calculated for the odds ratio (OR), 95% confidence interval (CI) and corresponding p-values, controlling for age as covariables. For all statistical tests, A p-value of $p<0.05$ was taken as significant.

Table 2. Demographics and Clinical Variables in Controls and RA

	Female patients with RA (n=153)	Female controls (n=96)
Age (years, mean±S.D.)	49.3±5.4	68.9±5.4
Disease duration (years, mean±S.D.)	4.68±3.53	
Erythrocyte sedimentation rate (mm/hr)	37.77±26.52	
C-reactive protein (mg/dL)	2.23±6.18	
Patients with bone erosion (n)	73	

Results

1. Clinical characteristics of RA in the female Korean

Clinical characteristics of RA patients and control subjects are shown in Table 2. One hundred fifty three female RA patients and 96 female healthy controls were recruited for this study. The mean age in RA patients was 49.3±5.4 years and control subjects 68.9±5.4. The mean disease duration was 4.68±3.53 years. ESR in RA patients was 37.77±26.52 (mm/hr) and CRP was 2.23±6.18 (mg/dL). Seventy three of a total of 153 RA patients exhibited bone erosion (47%).

2. Association between GnRH1 polymorphisms and RA

To assess whether polymorphisms of GnRH1 have any correlation with the risk of rheumatoid arthritis, genotype frequencies of 5 SNPs (rs2659590, rs2321248, rs6186, rs6185 and rs2321049) were examined in 153 rheumatoid arthritis and 96 control subjects, and multiple logistic regression analysis with adjustment for age was done.

Genotype distributions of 5 polymorphisms in this study were in Hardy-Weinberg equilibrium ($p>0.05$ data not shown). Genotype distributions and allele frequency of 5 SNPs in RA and control subjects are revealed in Table 2 (Table 3). Among 5 SNPs, rs6186 was monomorphic SNP. There was no significant association with RA in genotype distribution and allele frequency between RA female patients and controls (Table 3).

3. Associations between GnRH1 Polymorphisms and parameters of disease activity

As phenotyping stratification, association between polymorphisms

Table 3. Genotype Distributions and Allele Frequencies of Each Polymorphism of the *GnRH1* in the RA and Control Groups

Polymorphism	Subjects	Genotype distribution (frequency)				Allele frequency		
		11	12	22	p	1	2	p
rs2659590 (A>G)	RA	62 (0.41)	71 (0.47)	19 (0.12)	0.527	0.64	0.36	0.679
	Controls	26 (0.29)	50 (0.55)	15 (0.16)		0.56	0.44	
rs2321248 (G>A)	RA	134 (0.88)	18 (0.12)	0 (0.00)	0.758	0.94	0.06	0.438
	Controls	77 (0.87)	12 (0.13)	0 (0.00)		0.93	0.07	
rs6186 (G>A)	RA	152 (1.00)	0 (0.00)	0 (0.00)	1	1.00	0.00	1
	Controls	95 (1.00)	0 (0.00)	0 (0.00)		1.00	0.00	
rs6185 (C>G)	RA	52 (0.35)	70 (0.48)	25 (0.17)	0.822	0.59	0.41	0.912
	Controls	23 (0.26)	48 (0.54)	18 (0.20)		0.53	0.47	
rs2321049 (A>G)	RA	60 (0.40)	69 (0.46)	22 (0.15)	0.773	0.63	0.37	0.869
	Controls	27 (0.30)	52 (0.57)	12 (0.13)		0.58	0.42	

Table 4. Genotype Distributions and Allele Frequencies of Each Polymorphism of the *GnRH1* in the ESR<30 and ESR≥30 Groups of RA

Polymorphism	Subjects	Genotype distribution (frequency)				Allele frequency		
		11	12	22	p	1	2	p
rs2659590 (A>G)	ESR≥30	33 (0.38)	39 (0.44)	16 (0.18)	0.327	0.60	0.40	0.279
	ESR<30	28 (0.45)	31 (0.50)	3 (0.05)		0.70	0.30	
rs2321248 (G>A)	ESR≥30	72 (0.82)	16 (0.18)	0 (0.00)	0.458	0.91	0.09	0.438
	ESR<30	60 (0.97)	2 (0.02)	0 (0.00)		0.98	0.02	
rs6185 (C>G)	ESR≥ 30	24 (0.28)	45 (0.52)	18 (0.21)	0.222	0.53	0.47	0.112
	ESR<30	27 (0.47)	24 (0.41)	7 (0.12)		0.67	0.33	
rs2321049 (A>G)	ESR≥30	32 (0.37)	39 (0.45)	16 (0.18)	0.822	0.59	0.41	0.869
	ESR<30	27 (0.44)	29 (0.47)	6 (0.09)		0.67	0.33	

Table 5. Logistic Regression Analysis of 3 SNPs in *GnRH1* between the ESR<30 and ESR ≥30 Groups of RA

SNP	Model	OR	95% CI		p
			LCL	UCL	
rs2659590	Co-Dominant	1.61	0.98	2.65	0.058
	Dominant	1.37	0.71	2.66	0.35
	Recessive	4.37	1.21	15.72	0.011
rs6185	Co-Dominant	1.79	1.09	2.95	0.019
	Dominant	2.29	1.14	4.59	0.02
	Recessive	1.90	0.74	4.89	0.17
rs2321049	Co-Dominant	1.39	0.86	2.24	0.18
	Dominant	1.33	0.68	2.58	0.41
	Recessive	2.10	0.77	5.73	0.13

and biomarker, ESR and bone erosion was compared as parameters of disease activity.

ESR between the ESR 30< and ≥30 was compared (Table 4). Of the five SNPs, 2 SNPs were significantly associated with the risk of RA: rs2659590, OR=4.37, 95% CI=1.21-15.72, p=0.011 in the recessive model; rs6185, OR=1.79, 95% CI=1.09-2.99, p=0.019 in the codominant model and OR=2.29, 95% CI=1.14-4.59, p=0.02 in the dominant model; respectively (Table 5). In the case of rs2321248, there was significant association with ESR level in the G/A genotype; OR=6.67, 95% CI= 1.47-30.16, p=0.0028. Existence of bone erosion was also compared in RA patients. There were no significance in the genotype distribution and allele frequency between bone erosion (Table 6).

4. Associations between *GnRH1* Haplotypes and ESR parameter in disease activity

Three among 5 SNPs formed LD block. Haplotypes (frequency > 0.01) in the LD block were analyzed using HapAnalyzer software 1.0.[18]

Four haplotype were shown. On the haplotype association test, haplotypes, CAG and TGG, showed a significant association between the ESR < 30 and ESR 30 RA patients, respectively (Table 7).

Discussion

RA is a common autoimmune disease with a complex etiology in which genetic and environmental factors contribute to disease. The genetic component of RA is largely undefined and, up until very recently, there were only two reproducible associations. The strongest of these associations is of genes within the HLA region, particularly the HLA-DRB1 gene.[19] A second, more modest, association identified has been of the protein tyrosine phosphatase non-receptor 22 (PTPN22) gene.[20,21] In this study, we demonstrated that whether GnRH1 gene polymorphisms are associated with RA. There was no association between RA susceptibility and GnRH1 in female population.

Altogether the genetics of RA susceptibility has made enormous progress during the past years. In contrast, the field of the genetics of RA severity is relatively unexplored. Radiological joint damage is conceived as the most objective measure to determine the severity of RA. The number of studies investigating the relation between joint destruction and genetic variants is limited. Some SNPs are observed to associate with the disease outcome, but none of these associations are convincingly replicated in independent cohorts. Moreover, although a recent twin study indicated that genetic factors play a role in determining the severity of RA,[22] the heritability of the level of joint destruction (the variance of joint destruction that can be ascribed to genetic factors) is still unknown.

Joint damage in RA is highly variable between patients and the cumulative level is associated with the level of (persistent) inflammation. Nonetheless, several studies have provided evidence for

Table 6. Genotype Distributions and Allele Frequencies of Each Polymorphism of the *GnRH1* in the Existence of Bone Erosion of RA

Polymorphism	Subjects	Genotype distribution (frequency)				Allele frequency		
		11	12	22	p	1	2	p
rs2659590 (A>G)	Yes	32 (0.44)	32 (0.44)	9 (0.12)	0.827	0.66	0.34	0.979
	No	29 (0.38)	38 (0.49)	10 (0.13)		0.62	0.38	
rs2321248 (G>A)	Yes	65 (0.89)	8 (0.11)	0 (0.00)	0.958	0.95	0.05	0.938
	No	67 (0.87)	10 (0.13)	0 (0.00)		0.94	0.06	
rs6185 (C>G)	Yes	25 (0.35)	37 (0.51)	25 (0.35)	0.822	0.6	0.4	0.912
	No	26 (0.36)	32 (0.44)	15 (0.21)		0.58	0.42	
rs2321049 (A>G)	Yes	32 (0.44)	31 (0.43)	9 (0.12)	0.822	0.66	0.34	0.869
	No	27 (0.35)	37 (0.48)	13 (0.17)		0.59	0.41	

Table 7. Haplotype Analysis Consisting of Significant Polymorphisms in the Genes between the ESR<30 and ESR≥30 Groups of RA

Haplotype	Frequency	Case, control ratios	Chi square	p value
TGA	0.616	103.9 : 72.1, 81.0 : 43.0	1.203	0.2728
CGG	0.293	54.9 : 121.1, 33.0 : 91.0	0.751	0.3862
CAG	0.06	16.0 : 160.0, 2.0 : 122.0	7.213	0.0072
TGG	0.024	1.1 : 174.9, 6.0 : 118.0	5.689	0.0171

incomplete coupling between inflammation and destruction, which suggests that other individual factors also play a role. This suggestion leads to the hypothesis that candidate genes for the severity of RA are, on the one hand, genes that regulate the level of (local) inflammation and, on the other, genes that mediate the process of bone/cartilage destruction or bone regeneration. Gómez-Vaquero et al.[23] found significant difference in HAQ scores, ESR, current and accumulated dose of glucocorticoids, and number of disease modifying antirheumatic drugs taken, and lower serum hemoglobin and albumin according to the *BsmI VDR* gene polymorphisms. For the association analysis of RA-related phenotypes, we assessed whether GnRH1 polymorphisms are related to laboratory markers of disease activity such as ESR and bone erosion. Based on ESR (30 mm/hr) and the existence of bone erosion, we divided the RA patients into two clinical subgroups and analyzed the relationship between clinical data of RA and GnRH1 polymorphisms. Significant genetic associations were found between GnRH1 polymorphisms and clinical data of RA, such as ESR. RA patients were slightly less likely to have elevated ESR/low CRP.[24] Infection, renal insufficiency, and low albumin were associated with having elevated ESR/low CRP; low albumin predicted elevated CRP/low ESR and elevated ESR/low CRP discordance. RA patients were less likely to have elevated ESR/depressed CRP. ESR as a measure inflammation in systemic rheumatic disease may be limited in settings of infection, renal insufficiency, and low albumin.

GnRH plays an important role in immune system modulation. GnRH and its receptor are produced locally by immune cells, suggesting an autocrine role for GnRH. Several studies showed that exogenous GnRH stimulates actions in immune response, such as increase the levels of interleukin (IL)-2 receptor, interferon-γ (IFN-γ) and T helper cells. Jacobson et al.[13] suggested that GnRH might play a role in the exacerbation of autoimmune disorders. They assessed disease severity in intact and castrated, male and female, systemic lupus erythematosus (SLE)-prone (SWR×NZB) F1 hybrid mice during treatment with a GnRH agonist and antagonist. After 12 weeks of GnRH antagonist administration, total serum levels of IgG and anti-DNA antibodies were reduced, severity of renal disease decreased and survival improved significantly. On the other hand, they also demonstrated sexually dimorphic actions (disease severity was higher in females) of GnRH agonist. Based on their data, these results may partially explain gender differences in immune function.

Summary

In summary, the present study suggests that GnRH1 polymorphisms might not be associated with susceptibility to RA in female population. However, this study suggests that GnR1 gene polymorphisms may play a relevant role in the susceptibility to severity of ESR level in female RA patients. Additional studies, with a larger number of patients and in different populations, may be required to assess whether GnRH1 polymorphisms and these haplotype could be used as susceptibility or resistance markers in RA disease. This study is the first to analyze the association between SNPs of GnRH1 and RA, and may contribute to future studies on GnRH1.

References

1. van der Helm-van Mil AH, Breedveld FC, Huizinga TW. Aspects of early arthritis. Definition of disease states in early arthritis: remission versus minimal disease activity. Arthritis Res Ther. 2006;8:216.
2. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther. 2009;11:229.
3. Gerosa M, De Angelis V, Riboldi P, Meroni PL. Rheumatoid arthritis: a female challenge. Womens Health (Lond Engl). 2008;4:195-201.
4. Silverman MN, Sternberg EM. Neuroendocrine-immune interactions in rheumatoid arthritis: mechanisms of glucocorticoid resistance. Neuroimmunomodulation. 2008;15:19-28.
5. Graff RJ, Lappé MA, Snell GD. The influence of the gonads and adrenal glands on the immune response to skin grafts. Transplantation. 1969;7:105-11.
6. Millar RP, Lu ZL, Pawson AJ, Flanagan CA, Morgan K, Maudsley SR. Gonadotropin-releasing hormone receptors. Endocr Rev. 2004;25:235-75.
7. Fink G. Oestrogen and progesterone interactions in the control of gonadotrophin and prolactin secretion. J Steroid Biochem. 1988;30:169-78.
8. Chen ZG, Yu KL, Zheng HM, Dong KW. Estrogen receptor-mediated repression of gonadotropin-releasing hormone (gnRH) promoter activity in transfected CHO-K1 cells. Mol Cell Endocrinol. 1999;158:131-42.
9. Emanuele NV, Emanuele MA, Tentler J, Kirsteins L, Azad N, Lawrence AM. Rat spleen lymphocytes contain an immunoactive and bioactive luteinizing hormone-releasing hormone. Endocrinology. 1990;126:2482-6.
10. Maier CC, Marchetti B, LeBoeuf RD, Blalock JE. Thymocytes express a mRNA that is identical to hypothalamic luteinizing hormone-releasing hormone mRNA. Cell Mol Neurobiol. 1992;12:447-54.
11. Weesner GD, Becker BA, Matteri RL. Expression of luteinizing hormone-releasing hormone and its receptor in porcine immune tissues. Life Sci. 1997;61:1643-9.
12. Batticane N, Morale MC, Gallo F, Farinella Z, Marchetti B. Luteinizing hormone-releasing hormone signaling at the lymphocyte involves stimulation of interleukin-2 receptor expression. Endocrinology. 1991;129:277-86.
13. Jacobson JD, Nisula BC, Steinberg AD. Modulation of the expression of murine lupus by gonadotropin-releasing hormone analogs. Endocrinology. 1994;134:2516-23.
14. Livak KJ. Allelic discrimination using fluorogenic probes and the 5' nuclease assay. Genet Anal. 1999;14:143-9.
15. Solé X, Guinó E, Valls J, Iniesta R, Moreno V. SNPStats: a web tool for the analysis of association studies. Bioinformatics. 2006;22:1928-9.
16. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 2005;21:263-5.
17. Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. Am J Hum Genet. 2001;68:978-89.
18. Inform G. HapAnalyzer: minimum haplotype analysis system for association studies. Genomics Inform. 2004;2:107-9.
19. Newton JL, Harney SM, Timms AE, et al. Dissection of class III major histocompatibility complex haplotypes associated with rheumatoid arthritis. Arthritis Rheum. 2004;50:2122-9.
20. Hinks A, Barton A, John S, et al. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene. Arthritis Rheum. 2005;52:1694-9.
21. Plenge RM, Padyukov L, Remmers EF, et al. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. Am J Hum Genet. 2005;77:1044-60.
22. van der Helm-van Mil AH, Kern M, Gregersen PK, Huizinga TW. Variation in radiologic joint destruction in rheumatoid arthritis differs between monozygotic and dizygotic twins and pairs of unrelated patients. Arthritis Rheum. 2006;54:2028-30.
23. Gómez-Vaquero C, Fiter J, Enjuanes A, Nogués X, Díez-Pérez A, Nolla JM. Influence of the BsmI polymorphism of the vitamin D receptor gene on rheumatoid arthritis clinical activity. J Rheumatol. 2007;34:1823-6.
24. Costenbader KH, Chibnik LB, Schur PH. Discordance between erythrocyte sedimentation rate and C-reactive protein measurements: clinical significance. Clin Exp Rheumatol. 2007;25:746-9.

한국인 여성 류마티스성 관절염 환자에서 *GnRH1* 다형성 유전자 발현의 연관성

김유미[†,‡] • 한계영* • 곽은비[†] • 전완주[†] • 김성수[†] • 이희제[†]

강원대학교 의학전문대학원 *정형외과학교실, [†]약리학교실, [‡]원광대학교 정형외과학교실 산본병원

목적: 류마티스 관절염(RA)의 병태생리에 대해 아직 명확하게 밝혀져 있지 않으나 일부의 경우 유전적 요인이 류마티스 관절염의 발생에 영향을 주는 것으로 알려져 있다. 역학조사 결과 여성이 남성보다 류마티스성 관절염의 유병률이 3배 정도 높다. Gonadal 호르몬들은 면역체계나 자가면역질환에서 성에 따른 이형을 나타내는데 영향을 주는 것으로 알려져 있다. 이 가운데 gonadotrophin-releasing hormone (GnRH)는 면역 시스템을 조절하는 데도 중요한 역할을 한다. 따라서, GnRH가 류마티스 관절염에서 성적 차이를 나타내는데 중요한 역할을 할 수 있으며 이를 증명하기 위해 GnRH1 유전자를 후보 유전자로 선택하고 이들 유전자 내의 단일염기다형성(SNP)을 분석함으로써, RA와 GnRH1 유전자 다형성과의 연관성에 대해 연구하고자 하였다.

대상 및 방법: 153명의 RA 여성 환자와 96명의 정상 대조군을 대상으로, GnRH1 유전자 내의 5개의 SNP, rs2659590, rs2321248, rs6186, rs6185, rs2321049의 유전자형과 대립유전자형의 빈도를 비교 분석하였다. 또한 RA 환자들을 erythrocyte sedimentation rate (ESR)과 골 미란 유무에 따라 나누고 GnRH1 SNP과의 연관성을 확인하였다.

결과: 한국인 여성 RA 환자들과 정상군들 사이에서 GnRH1 SNP들의 유전자형과 대립유전자들의 빈도는 유의한 차이가 없었다. 하지만, rs2659590, rs6185, rs2321248에서 ESR이 30 이상인 환자와 30 미만 환자 사이에 로지스틱 회귀 분석 결과 유의한 상관관계가 나타났다. 하지만, 골 미란 유무는 연관성이 없었다.

결론: 본 연구에서 RA와 GnRH1 유전자 다형성 사이의 연관성은 보여주지 못하였지만, ESR의 수치와 GnRH1 유전자 다형성 간에 연관성을 보였다. 비록 그 수가 적어 제한적인 의미를 가질 수 있으나, 처음으로 GnRH1 유전자의 다형성과 RA환자의 ESR 간의 연관 가능성을 시사하는데 의의가 있다.

색인단어: GnRH1, 류마티스성 관절염, 단일염기다형성, 연합연구

접수일 2009년 12월 30일 **게재확정일** 2010년 7월 1일

교신저자 이희제, 강원도 춘천시 효자동, 강원대학교 의학전문대학원 약리학교실

TEL 033-250-8850, **FAX** 033-255-8809, **E-mail** heejaelee@kangwon.ac.kr