ORIGINAL ARTICLE

Increased Prevalence of Interleukin-1 Receptor Antagonist Gene Polymorphism in Patients With Chronic Rhinosinusitis

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Objective: To assess the association of the interleukin (IL)-1β and the IL-1 receptor antagonist (IL-1Ra) gene polymorphisms with chronic rhinosinusitis (CRS).

Design: Genotyping of the 2 IL-1β gene (*IL1B*) polymorphisms (promoter and exon) and the IL-1Ra gene (*IL1RN*) polymorphism (intron 2) was performed using polymerase chain reaction and restriction length fragment polymorphism analyses.

Setting: Prospective study, tertiary medical center.

Patients: The study population comprised 88 consecutive adult Taiwan-Chinese patients who met stringent criteria for CRS and received endoscopic sinus surgery and 103 healthy volunteers of the same ethnicity and similar age range. Of the 88 patients, 61 had CRS with nasal polyps, while the other 27 had CRS without nasal polyps.

Results: There were significant differences in the distribution of the *IL1RN* polymorphism between the control subjects and patients with CRS ($P<.05$). The II allele of *IL1RN* occurred more frequently in the CRS patient group, and the odds ratio for subjects with *I/II* genotype was 3.39 (95% confidence interval, 1.25-9.18). In the case of CRS without nasal polyps, the odds ratio for subjects with *I/II* genotype was further increased to 4.75 (1.39-16.25). There was no association between the other 2 polymorphisms of *IL1B* and CRS.

Conclusion: Increased prevalence of *IL1RN* polymorphism in patients with CRS suggests that this polymorphism, or a polymorphism in linkage disequilibrium with it, may be involved in the development of CRS.

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CHRONIC RHINOSINUSITIS (CRS) is defined as "a condition manifested by an inflammatory response involving the mucous membranes of the nasal cavity and paranasal sinuses, fluids within these cavities, and/or underlying bone"[1]; it carries a significant personal and economic burden and is accompanied by decreased productivity and impaired quality of life.[2,3] Various models involving physiological and anatomical factors have been proposed to explain the etiology of this prevalent disease. Nevertheless, the cause and pathogenesis remain controversial.[3-6] More recently, the role of chronic inflammatory processes in the pathogenesis of CRS has been increasingly recognized.[1,3-5] The histopathologic features of CRS is characterized by thickening of the basement membrane, subepithelial fibrosis and edema, goblet cell hyperplasia, and persistent inflammation.[7] However, many reports of familial clustering of sinus disease implicate a genetic basis for CRS that is resistant to medical and surgical intervention. There is increasing evidence that both inflammatory and genetic factors may be involved in the development of CRS.[8-10]

Interleukin (IL)-1, one of the most important proinflammatory cytokines, is a potent transmitter between cells during inflammatory reactions.[11] Interleukin-1β as well as tumor necrosis factor (TNF) were reported to up-regulate the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which enhances leukocyte infiltration into the nasal mucosa.[12] The genes in the IL-1 complex code for 3 proteins, IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra). In contrast to the α form, the IL-1β molecule is mainly secreted by the cells, and its plasma levels are often elevated in various diseases.[13] Different polymorphisms have been described in the IL-1β gene (*IL1B*), and at least 2 of them are known to influence protein production: one is located within the promoter region at position -511 and the other in exon 5.[14] Moreover, the IL-1β gene is situated on chro-

Table 1. Case and Control Demographics, Allergy Results, and Clinical Information

Variable	CRS (n = 88)	Control (n = 103)	*P* Value
Age, mean ± SD, y	43.8 ± 17.1	38 ± 12.8	>.05
Sex, M/F	57/31	59/44	>.05
Phenotype, No. (%)			
With or without NPs			
CRS with NPs	61 (69)	. . .	. . .
CRS without NPs	27 (31)	. . .	. . .
Nonatopic CRS	51 (58)	. . .	. . .

Abbreviations: CRS, chronic rhinosinusitis; NPs, nasal polyps.

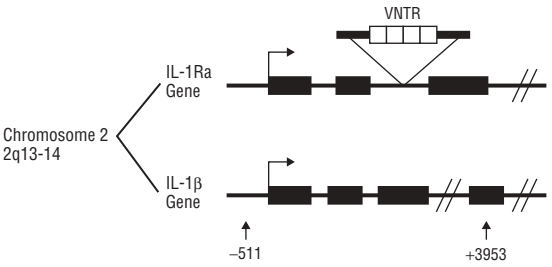

Figure. Diagram showing locations of the single base pair polymorphisms in the 5′ flanking region of the interleukin (IL)-1β gene. Numbers refer to base pairs 5′ of the transcription start site. The polymorphism in the IL-1Ra gene is a variable number tandem repeat (VNTR) of an 86–base pair segment in intron 2.

mosome 2 in close linkage with another gene of the IL-1 gene family that encodes for IL-1Ra. Linkage disequilibrium of the IL-1β and IL-1Ra genes during recombination may be one of the causes of the disease.[15] Interleukin 1Ra, the natural competitive inhibitor of IL-1, also plays an important role as a regulator of inflammation by occupying the IL-1 cell surface receptor.[16] There are 5 variable number tandem repeated polymorphisms in intron 2 of the IL-1Ra gene (*IL1RN*).[17] The I, II, III, IV, and V alleles correspond to 4, 2, 5, 3, and 6 copies of the 86–base pair repeated sequence, respectively. The variants of I and II allele of *IL1RN* are associated with altered production rates of IL-1Ra protein and may influence the variation of the intracellular signal pathway.[13,18]

Polymorphisms of the IL-1 genes have been shown to be associated with several inflammatory diseases, such as sepsis, rheumatoid arthritis, and asthma.[19-22] Believing that individuals with greater inflammatory responses may be more susceptible to inflammatory disease, we investigated whether there is an association between chronic rhinosinusitis and 2 polymorphisms in the IL-1β gene (promoter and exon 5) and 1 polymorphism in the IL-1Ra gene (intron 2).

METHODS

PATIENTS

The study population comprised 88 consecutive patients with a clinical diagnosis of CRS who underwent endoscopic sinus surgery by the senior authors (Y.-K.C., C.-D.L., and M.-H.T.) at China Medical University Hospital, Taichung, Taiwan, between July 2002 and December 2003. All patients received a thorough medical history taking and serial rhinologic examinations, including endoscopy and computed tomographic (CT) scan; patients with nasal diseases other than CRS or with a high index of suspicion for gastroesophageal reflux were excluded from our study.

The diagnosis of CRS was based on its definition by the American Academy of Otolaryngology–Head and Neck Surgery, which describes the typical symptoms that persist for 12 weeks or longer, and positive findings on CT scan showing opacification or swelling of the ethmoidal and maxillary mucosa and an obstruction of the ostiomeatal complex bilaterally but without polyp formation visible by preoperative nasal endoscopy or during surgery.[1] Bilateral nasal polyps were diagnosed based on history, clinical examination, nasal endoscopy, and sinus CT scan. Nasal polyposis was defined as presence of endoscopically visible bilateral polyps growing from the middle nasal meatus into the nasal cavities and affecting bilaterally more than 1 paranasal sinus according to the CT scan. Of the 88 patients, 61 were diagnosed as having CRS with nasal polyps and the remaining 27 as having CRS without nasal polyps (**Table 1**).

The allergic status was evaluated based on the measurement of serum total IgE level and the allergy screening test Phadiatop (Pharmacia CAP System, Uppsala, Sweden).[22,23] Total serum IgE levels and Phadiatop findings were analyzed by the fluoroenzyme immunoassay method in an accredited laboratory according to the manufacturer's instructions (Pharmacia CAP System). Subjects were considered nonatopic if they did not have Phadiatop positivity and had a serum IgE level lower than 100 IU/mL. Nonatopic subjects had negative skin test results and were symptom free.[24,25] In this context, 51 of the patients with CRS showed a negative result for atopy and were substratified as CRS patients without allergy (nonatopic).

The 88 enrolled adult Taiwanese patients (31 women and 57 men) ranged in age from 18 to 73 years, with a mean ± SD age of 43.8 ± 17.1 years; all patients were unrelated and had recalcitrant CRS without evidence of fungal infection, cystic fibrosis, or mucociliary disorders. The 103 CRS-free, unrelated control volunteers (44 women and 59 men) were from the same area as study group members and ranged in age from 20 to 70 years, with a mean ± SD age of 38 ± 12.8 years; all of them were examined by the same physician in the same fashion, including IgE serology, CT scan, and endoscopy. This study was reviewed by the institutional review board of the China Medical University Hospital. Informed consent was obtained from all patients who participated in this study.

GENOTYPING

We investigated 3 gene polymorphisms, *IIL1B* promoter (–511 C→T substitution), *IL1B* exon (+3953 C→T substitution) and *IL1RN* (intron 2, variable number tandem repeat) (**Figure**). Details of these polymorphisms and allele definition are listed in **Table 2**. The genomic DNA was prepared from peripheral blood by a Genomaker reagent kit (Blossom, Taichung). Polymerase chain reaction isolated the genotypes of all 3 IL-1–related genes. Restriction length fragment polymorphism for the 2 loci, *IL1B* promoter and *IL1B* exon, were studied. Primers and polymerase chain reaction conditions for the *IL1B* promoter, *IL1B* exon, and *IL1RN* polymorphisms are also listed in Table 2, according to the reports by Cantagrel et al[20] and Hang et al.[26] Polymerase chain reaction amplification was performed in a programmable thermal cycler GeneAmp PCR System 2400 (PerkinElmer, Wellesley, Mass). Genotypes were scored by investigators blinded to clinical phenotype. The prevalence of these polymorphisms was compared between the CRS group and the control group.

Table 2. Details of Polymorphisms and PCRs Used for Screening

Variable	*IL1B* Promoter	*IL1B* Exon	*IL1RN*
Type of polymorphism	Single base C→T	Single base C→T	86-bp VNTR
Site of polymorphism	Position –511	Exon 5	Intron 2
Allele definition	C allele = cytosine at –511; T allele = thymine at –511	E1 allele = cytosine at +3953; E2 allele = thymine at +3953	I allele = 4 repeats; II allele = 2 repeats; III allele = 5 repeats; IV allele = 3 repeats; V allele = 6 repeats
PCR primers			
Upstream	5′-TGGCATTGATC-TGGTTCATC-3′	5′-GTTGTCATCAG-ACTTTGACC-3′	5′-CTCAGCAA-CACTCCTAT-3′
Downstream	5′-GTTTAGGAATC-TGGACCAGA-3′	5′-TTCAGTTCATA-TGGACCAGA-3′	5′-TCCTGGTCT-GCAGGTAA-3′
PCR conditions			
Denaturation	95°C, 30 s	95°C, 30 s	95°C, 30 s
Annealing	55°C, 30 s	55°C, 30 s	58°C, 30 s
Extension	72°C, 30 s	72°C, 30 s	72°C, 30 s
No. of cycles	30	30	35
Digestion	Yes (*Ava* I)	Yes (*Tag* I)	No
PCR product size	C allele = 190 + 114 bp; T allele = 304 bp	E1 allele = 135 + 114 bp; E2 allele = 249 bp	I allele = 410 bp; II allele = 240 bp; III allele = 500 bp; IV allele = 325 bp; V allele = 595 bp

Abbreviations: bp, base pairs; PCR, polymerase chain reaction.

STATISTICAL ANALYSIS

The genotype frequencies distributions of these polymorphisms in the control and CRS patient groups were compared by the χ^2 test. When the assumption of the χ^2 test was violated (ie, when 1 cell had an expected count of <1% or >20% of the cells had an expected count of <5%), the Fisher exact test was used. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined for disease susceptibility of specific alleles in the polymorphism of IL-1Ra gene. Results were considered statistically significantly when the probability of findings occurring by chance was less than 5% ($P<.05$). Performing power analysis and sample size estimation is an important aspect of experimental design; therefore, the power of the designed experiment was also calculated by SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Ill). The result of the calculation was 89.8%, which indicates the sample size is not too low and the experiment will not lack the precision to provide reliable answers to the questions it is investigating.

Table 3. Distribution of *IL1B* Promoter and *IL1B* Exon Polymorphism Between Control Subjects and Patients With CRS*

Genotype	Patients With CRS	Control Subjects	*P* Value
IL1B promoter			
C/C	23 (26)	27 (27)	.69†
C/T	48 (55)	51 (50)	
T/T	17 (19)	25 (24)	
Total	**88 (100)**	**103 (100)**	
IL1B exon			
E1/E1	86 (98)	98 (95)	.29‡
E1/E2	2 (2)	5 (5)	
E2/E2	0	0	
Total	**88 (100)**	**103 (100)**	

Abbreviation: CRS, chronic rhinosinusitis.
*Data are given as number (percentage) of subjects unless otherwise specified. Percentages may not add to 100 because of rounding.
†χ^2 Test.
‡Fisher exact test.

RESULTS

The distribution of the *IL1B* promoter and *IL1B* exon polymorphism and the corresponding genotype frequencies are given in **Table 3**. There was no significant difference between the patients with CRS and the control subjects. In **Table 4**, the distribution of the *IL1RN* genotype in the control group revealed 95 I/I allele homozygotes (92%), 6 I/II allele heterozygotes (6%), 1 II/II allele homozygote (1%), and 1 IV/IV allele homozygote (1%). The distribution of the *IL1RN* genotype in the CRS group showed 70 I/I allele homozygotes (80%), 15 I/II allele heterozygotes (17%), 1 II/II allele homozygote (1%), and 2 I/IV allele heterozygotes (2%). There were significant differences in the distribution of the IL-1Ra gene polymorphism between the patients with CRS and the control subjects ($P<.05$). To analyze a possible polymorphism in linkage disequilibrium, only the number of persons carrying *I/I* or *I/II* genotypes were counted, while persons carrying *II/II*, *I/IV*, or *IV/IV* genotypes were excluded because of their low number. The *I/II* genotype occurred more frequently in the patients with CRS than in healthy controls, with an OR of 3.39 (95% CI, 1.25-9.18). An age-adjusted test for the *I/I* and *I/II* genotypes of *IL1RN* polymorphism indicated that age did not influence the result (OR, 2.87; 95% CI, 1.05-7.89). The results suggest that only the distribution of the IL-1Ra gene polymorphism was significantly different between the control group and the patients with CRS. There was no association between the other 2 polymorphisms of the IL-1β gene and CRS.

Table 4. Distribution of *IL1RN* Polymorphism Between Control Subjects and Patients With CRS*

IL1RN Genotype	Patients With CRS	Control Subjects	*P* Value
I/I	70 (80)	95 (92)	.01†
I/II	15 (17)	6 (6)	
II/II	1 (1)	1 (1)	
I/IV	2 (2)	0	
IV/IV	0	1 (1)	
Total	**88 (100)**	**103 (100)**	

Abbreviation: CRS, chronic rhinosinusitis.
*Data are given as number (percentage) of subjects unless otherwise specified.
†Fisher exact test.

We also studied the subgroups of patients with CRS of various etiologic factors. For patients with or without nasal polyps, the distributions of the *IL1B* promoter, *IL1B* exon, and *IL1RN* polymorphism were compared with control subjects (**Table 5**). There were significant differences only in the distribution of the IL-1Ra gene polymorphism between the patients with CRS without nasal polyps and the control subjects ($P<.05$) (Table 5). This was mainly because of the increased number of *I/II* genotypes among patients with CRS without nasal polyps than among control subjects, with an OR of 4.75 (95% CI, 1.39-16.25); the OR was 4.26 for II allele frequency (95% CI, 1.31-13.82). Of CRS patients without allergy, the frequency distribution of IL-1Ra and IL-1β genotypes is listed **Table 6**, which indicated there was no significant difference between the nonatopic patients with CRS and the control subjects.

COMMENT

Our results suggest that the frequency of II allele of the IL-1Ra gene polymorphism is significantly higher in Taiwanese patients with CRS than in the control subjects. No significant association was identified in the distributions of *IL1B* genotype with CRS subgroups, although IL-1β has been proposed to play a role in the development of nasal polyps.[27,28] In our control group, the allelic frequencies of the *IL1B* promoter were similar with those previously reported in other healthy controls.[13,17] However, there was a relatively low incidence of the II allele of the *IL1RN* polymorphism and the E2 allele of the *IL1B* exon polymorphism in our control group. Population differences could be a contributing factor.

The IL-1Ra gene lies within the IL-1 gene cluster, on chromosome 2 (q14-q21), close to the IL-1α and IL-1β genes that mediate inflammation.[29] As observed in our study, III, IV, and V alleles are uncommon and account for less than 5%.[13,17] Because there are 3 potential protein-binding sites located within the repeated sequence, the number of repeats may influence gene transcription and protein production.[30,31] Because proinflammatory responses elicited by IL-1β could be down-regulated by IL-1Ra, decreased production of IL-1Ra might be a significant predisposing factor to the chronicity of an inflammatory disease. Moreover, increased frequency of the II allele of this polymorphism has also been previously found to be associated with a variety of chronic inflammatory diseases, such as systemic lupus erythema,[15] inflammatory bowel diseases,[14,32] and asthma.[21,22]

Table 5. Distribution of *IL1B* and *IL1RN* Polymorphisms Between Control Subjects and Patients With CRS With or Without Nasal Polyps*

Genotype	Patients With CRS	Control Subjects	*P* Value
IL1B promoter			
C/C	16 (26)	27 (27)	.77†
C/T	33 (54)	51 (50)	
T/T	12 (20)	25 (24)	
Total	**61 (100)**	**103 (100)**	
IL1B exon			
E1/E1	59 (97)	98 (95)	.48‡
E1/E2	2 (3)	5 (5)	
E2/E2	0	0	
Total	**61 (100)**	**103 (100)**	
IL1RN			
I/I	50 (82)	95 (92)	.09‡
I/II	9 (15)	6 (6)	
II/II	1 (2)	1 (1)	
I/IV	1 (2)	0	
IV/IV	0	1 (1)	
Total	**61 (100)**	**103 (100)**	
IL1B promoter			
C/C	7 (26)	27 (27)	.79†
C/T	15 (56)	51 (50)	
T/T	5 (19)	25 (24)	
Total	**27 (100)**	**103 (100)**	
IL1B exon			
E1/E1	27 (100)	98 (95)	.31‡
E1/E2	0	5 (5)	
E2/E2	0	0	
Total	**27 (100)**	**103 (100)**	
IL1RN			
I/I	20 (74)	95 (92)	.02‡
I/II	6 (22)	6 (6)	
II/II	0	1 (1)	
I/IV	1 (4)	0	
IV/IV	0	1 (1)	
Total	**27 (100)**	**103 (100)**	

Abbreviation: CRS, chronic rhinosinusitis.
*Data are given as number (percentage) of subjects unless otherwise specified. Percentages may not add to 100 because of rounding.
†χ^2 Test.
‡Fisher exact test.

The association of sinusitis and asthma with histopathologic features, disease severity, and therapeutic outcome was recognized for a long time, and many studies indicated that the association reflects a systemic inflammatory process of respiratory mucosa.[33-35] Mao et al[22] conducted a genetic association study in a Japanese population to test whether variants of IL-1 relate to asthma. They found that the II allele of *IL1RN* is associated with nonatopic asthma. This allele is strongly associated with lower IL-1Ra levels, which may promote chronic inflammatory reaction induced by IL-1β in nonatopic asthma.

Chronic rhinosinusitis has diverse etiologic factors. It could be divided into CRS with or without nasal polyposis because these 2 have been shown to have differ-

ent types of inflammatory cells and different levels of inflammatory cytokines.[5] In this regard, we examined the distributions of the 3 polymorphisms in the 2 subgroups of patients with CRS compared with control subjects. There were significant differences in the distribution of the *IL1RN* polymorphism between the patients with CRS without nasal polyps and the control subjects; there were no significant differences between the patients with CRS with nasal polyps and the control subjects. The different results from the 2 subgroups of patients with CRS could also provide a genetic basis, to a certain extent, for such a classification of CRS.

There are numerous factors contributing to the pathogenesis and chronicity of CRS, including genetics, anatomic anomalies, bacteria, and fungus. Allergic rhinitis, cystic fibrosis, mucociliary disorders, and gastroesophageal reflux are also thought to affect the presentation of the disease.[36-39] Nevertheless, almost of all these complexities could be simplified by stringent screening and by classifying patients during history taking, imaging, physical and laboratory examinations, operative finding, and pathological review. Because single nucleotide substitutions in several genes have been reported to be associated with allergic diseases,[40,41] we subgrouped patients with CRS and focused on patients with CRS without allergy (nonatopic CRS) to test if variants of *IL1RN* related to CRS. However, no significant difference was seen in the frequencies of IL-1Ra and IL-1β genotypes compared with the control subjects.

Chronic rhinosinusitis is a common chronic illness. It is likely that inflammation and genetics are both essential mechanisms in the pathogenesis of CRS. A better understanding of the cause and pathophysiologic mechanisms of CRS at the molecular level may provide new guides for diagnosis and therapeutic strategies.[10] Both IL-1β and IL-1Ra are cytokines that play key roles in immune responses, inflammation, and fibrosis. Single nucleotide polymorphisms have important implications in human genetic research, and an understanding of the polymorphisms associated with CRS is expected to increase the comprehension of the course of the disease. While a genetic association between a variant of IL-1α with nasal polyps in patients with asthma has been identified,[21] to our knowledge, no intensive study on polymorphisms of *IL1B* and *IL1RN* in relation to CRS was reported to date. We found that the II allele of *IL1RN* occurred more frequently in patients with CRS than in healthy patients. This allele might be associated with lower IL-1Ra levels, which may promote chronic inflammatory reaction induced by IL-1β in CRS. However, the prevalence of the one polymorphism shown to be statistically associated with the chronic sinusitis phenotype was low. Thus, while 17% of patients with CRS expressed a particular set of alleles for the IL-1Ra gene (and this was statistically significant), this level of association implies that if such a genotype plays a role in the pathogenesis of the disease, it could be operating in the minority of cases. Further studies should be conducted to clarify this polymorphism with disease severity or with in vitro gene expression, such as serum levels of IL-1Ra.

In conclusion, our data demonstrate an increased prevalence of *I/II* heterozygotes of the IL-1Ra gene polymorphism in a Taiwanese population of patients with CRS compared with control subjects. This implies that this polymorphism, or a variant in linkage disequilibrium with it, may be involved in determining the genetic susceptibility and pathogenesis of CRS. However, the underlying mechanism of the association needs to be clarified in the future.

Table 6. Distribution of *IL1B* and *IL1RN* Polymorphisms Between Control Subjects and Patients With Nonatopic Chronic Rhinosinusitis*

Genotype	CRS Without Allergy	Control Subjects	*P* Value
IL1B promoter			
C/C	15 (29)	27 (27)	.64†
C/T	27 (53)	51 (50)	
T/T	9 (18)	25 (24)	
Total	**51 (100)**	**103 (100)**	
IL1B exon			
E1/E1	50 (98)	98 (95)	.35‡
E1/E2	1 (2)	5 (5)	
E2/E2	0	0	
Total	**51 (100)**	**103 (100)**	
IL1RN			
I/I	44 (86)	95 (92)	.19‡
I/II	5 (10)	6 (6)	
II/II	0	1 (1)	
I/IV	2 (4)	0	
IV/IV	0	1 (1)	
Total	**51 (100)**	**103 (100)**	

*Data are given as number (percentage) of subjects unless otherwise specified. Percentages may not add to 100 because of rounding.
†χ^2 test.
‡Fisher exact test.

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