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Association of *IL-1* gene polymorphisms with chronic rhinosinusitis with and without nasal polyp

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Conflict of Interest
The authors have no financial conflicts of interest.

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Conceptualization: Sakinah Mohamad. Data curation: Sakinah Mohamad. Formal analysis: Norasnieda Md Shukri. Funding acquisition: Sakinah Mohamad. Investigation: Sakinah Mohamad. Project administration: Ahmad Azlina. Resources: Ahmad Azlina. Supervision: Suzina Sheikh Ab Hamid, Ahmad Azlina.

ABSTRACT

Background: Chronic rhinosinusitis (CRS) is one of the most common and complex chronic inflammatory disease of sinonasal mucosa. Even though the pathogenesis of CRS is multifactorial and still unclear, the role of cytokines especially interleukin-1 (IL-1) is being investigated worldwide in different population because of varying results obtained.
Objective: To study the association of *IL-1* (*A* and *B*) gene polymorphisms with chronic rhinosinusitis with nasal polyp (CRSwNP) and without nasal polyp (CRSsNP), and other factors related.
Methods: This is a case-controlled study which include a total of 138 subjects recruited from Otorhinolaryngology-Head and Neck Surgery clinic in Hospital Universiti Sains Malaysia. Genotyping of the *IL-1A* (+4845G, +4845T) and *IL-1B* (−511C, −511T) were performed with restriction fragment length polymorphism analysis.
Results: There was a statistical significant association between *IL-1B* (−511C, −511T) polymorphism with CRSwNP and CRSsNP ($p < 0.001$). The CT genotype of *IL-1B* was markedly increased in CRSwNP subjects (52.2%). However, there was no significant association found between *IL-1A* (+4845G, +4845T) with CRSwNP and CRSsNP ($p = 0.093$). No association was found in factors related to CRS, which included asthma, atopy, allergy, aspirin sensitivity, and family history of nasal polyp (p value of 0.382, 0.382, 0.144, >0.95, and 0.254, respectively).
Conclusion: This study indicates an association of *IL-1B* (−511C, −511T) polymorphism with CRSwNP and CRSsNP in our population, hence there is a possibility of *IL-1B* involvement in modulating pathogenesis of CRS. There was no significant association of *IL-1A* (+4845G, +4845T) polymorphism with CRSwNP and CRSsNP, and other factors related.

Keywords: Rhinosinusitis; Nasal polyps; Interleukin-1; Single nucleotide polymorphism

INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common chronic inflammatory disease of sinonasal mucosa, affecting 15.5% of the total population in United States, making it the second most common condition of all chronic conditions [1]. The Global Allergy and

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Asthma Network of Excellence study revealed that the overall prevalence of CRS in the Europe countries was 10.9% [2], whereas the prevalence in the Asian countries was reported to be around 6.9% to 8.0% [3].

CRS can be further classified into 2 phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [4]. Histopathologically, nasal polyp is categorized by proliferation of the epithelial layer, thickening of the basement membrane, focal fibrosis, glandular hyperplasia, oedema, cellular infiltration of stromal layer and presence of inflammatory cells [5, 6]. It is usually bilateral and described as peeled grape-like, glistening, pale-grey, smooth, semitransparent mass with a pedicle arising from the osteomeatal-complex [7, 8]. Apart from the presence of polyp in the nasal cavity for CRSwNP, these patients were reported to have a higher frequency of nasal discharge, nasal obstruction and change in smell, as compared to CRSsNP patients who complain more of facial pain or headache [9].

CRS is a complex disease whereby the actual pathogenesis is still under active investigation and is believed to be of a multifactorial. The inflammatory reaction of the sinonasal mucosal lining causing mucosal oedema which obstructs the sinus ostia, leading to mucus retention and infection, hence development of CRS [10]. Among the predisposing factors associated with this disease are asthma, aspirin sensitivity, allergy, atopy, cigarette smoking and genetic factor [1]. It is also believed that CRS is affected by multiple genes that may interact with undetermined environmental factors and potentially cause disease expression [1].

Interleukin-1 (IL-1) is one of the most important proinflammatory cytokines as well as a potent transmitter between cells which modulates early in the cascade of inflammatory response in CRSwNP [11]. IL-1 plays a role in activating T lymphocytes and monocytes, and also upregulating expression of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 [6, 12]. *IL-1* exists in 3 forms namely *IL-1A*, *IL-1B*, and IL-1 receptor antagonist, which are located on the long arm of chromosome 2 [6].

Several studies conducted in different countries had proven that genetic polymorphisms of IL-1 have been contributed to development of CRS. Genetic polymorphism is defined as multiple alleles occur at a single locus, whereby at least 2 alleles present with a frequency greater than 1 percent [13]. Initially, Karjalainen et al. [14] demonstrated an association of *IL-1A* (+4845G, +4845T) with nasal polyp in asthmatic adults in Finnish population. Similar finding was subsequently found in CRS patients in Canadian population [6]. A Turkish study successfully reported association of both *IL-1A* (+4845G, +4845T) and *IL-1B* (−511C, −511T) polymorphisms with CRSwNP patients [5]. In contrast, Bernstein et al. [15] in United State showed no significant association of *IL-1A* and *IL-1B* in their CRSwNP patients. The contradictory results may suggest that variation between ethnic groups affecting frequency of many genetic alleles [16].

Besides CRS, studies shown that *IL-1* genetic polymorphisms is also associated with other inflammatory disease such as periodontitis, rheumatoid arthritis, inflammatory bowel disease, and gout [16-19]. Examples of IL-1 inhibitor available in clinical use are anakinra, canakinumab and rilonacept which are effective in the advanced treatment of gout [19].

To date, there is no such study done in Southeast population, the present study aimed to study the association of *IL-1A* and *IL-1B* genetic polymorphisms with CRSwNP and CRSsNP.

Besides that, we also attempted to determine the association of other factors (asthma, atopy, allergy, aspirin sensitivity, and family history of nasal polyp) related to CRSwNP and CRSsNP.

MATERIALS AND METHODS

Sample size calculation

Sample size calculation was determined by using Power and Sample software (ver. 3.0.43) based on previous literature by Karjalainen et al. [14] and Bernstein et al. [15]. The power of study used was 0.80 with level of statistically significant (α) of 0.05, meanwhile the probability of exposure among controls and cases were 0.40 and 0.70. Ten percent drop out was added to the largest sample size calculated making it 138 subjects in total (46 subjects in each group: CRSwNP, CRSsNP, and control).

Subjects

A case-controlled study was conducted with a total of 92 patients (46 CRSwNP patients and 46 CRSsNP patients) and 46 controls aged more than 18 years old were recruited from Otorhinolaryngology-Head and Neck Surgery clinic in Hospital Universiti Sains Malaysia. The diagnosis of CRS was based on clinical history and confirmed by direct visualisation via nasal endoscopy as proposed by the European Position Paper on Rhinosinusitis and Nasal Polyp (EPOS) [1] or those with history of polypectomy confirmed with pathology reports. Those with cystic fibrosis, Kartagener syndrome, Young syndrome, antrochoanal polyp, inverted papilloma, or any malignancy were excluded from the cases. The control group consisted of healthy individuals those who volunteered. They were not blood-related to the cases and living in the same district areas with the cases to minimise the environmental bias. They did not have any history of nasal symptoms, allergy, family history of allergy and any chronic inflammatory disorders.

A standardised questionnaire comprised of demographic characteristics (e.g., age at diagnosis, sex, ethnicity, and smoking history), duration of symptoms, nasal symptoms (according to EPOS 2012) [1], history of previous sinus surgery, predisposing factors of CRS (e.g., the presence of asthma, atopy, allergy, aspirin intolerance, and family history of nasal polyps) and nasoendoscopic findings were obtained from all subjects. During nasoendoscopy, presence of any polyp, grading of nasal polyp (according to Lund [20]), mucopurulent discharge or obstruction in the middle meatus, and mucosal oedema were recorded.

Deoxyribonucleic acid collection and extraction

Each patient's DNA was collected using a buccal swab and then stored at -20°C until DNA extraction was done. Then, the DNA extraction was performed using Exgene Blood SV Mini Kit (GeneAll, Seoul, Korea) by following the manufacturer's protocol.

Polymerase chain reaction and restriction fragment length polymorphism

The genotype of *IL-1A* (+4845G, +4845T) and *IL-1B* (−511C, −511T) were determined by polymerase chain reaction (PCR) amplification by using Master Cycler Vapo Protect (Eppendorf, Germany) with the primers as identified by Karjalainen et al. [14], then followed by restriction fragment length polymorphism. The primers used for *IL1A* and *IL1B* were as following: 5′-ATG GTT TTA GAA ATC ATC AAG CCT AGG GCA-3′ (forward primer) and 5′-AAT GAA AGG AGG GGA GGA TGA CAG AAA TGT-3′ (reverse primer); and 5′-TGGCATTGATCTGGTTCATC-3′ (forward primer) and 5′-GTTTAGGAATCTTCCCACTT-3′

(reverse primer), respectively. Then, for both genes, 1-μL forward primer, 1-μL reverse primer, 3-μL genomic DNA, 5-μL Dnase free water and 10-μL Phusion High-Fidelity PCR Master Mix with HF Buffer (New England Biolabs, Ipswich, MA, USA) were mixed together. The PCR cycling conditions were as follows: (1) For *IL-1A* (+4845G, +4845T) initial denaturation at 94°C for 3 minutes, 30 cycles of denaturation at 98°C for 60 seconds, annealing at 54°C for 60 seconds, extension at 72°C for 2 minutes and final extension at 72°C at 5 minutes; (2) For *IL-1B* (−511C, −511T): initial denaturation at 94°C for 10 minutes, 30 cycles of denaturation at 94°C for 45 seconds, annealing at 55°C for 45 seconds, extension at 72°C for 60 seconds, and final extension at 72°C at 10 minutes.

Subsequently, to detect *IL-1A* (+4845G, +4845T), digestion with restriction enzyme *Sat*I (New England Biolabs, Hitchin, UK) was performed after amplification to yield 124-, 76-, and 29-base pair (bp) bands in the presence of allele G, and 153- and 76-bp bands in the presence of allele T [5]. Whilst, to detect *IL-1B* (−511C, −511T), digestion with restriction enzyme *Ava*I (New England Biolabs, Hitchin, UK) is performed to yield 305-bp bands in the presence of allele C, and 190- and 115-bp bands in the presence of allele T [5]. Therefore, a 4.0-μL PCR product were digested with 0.5-μL respective restriction enzyme together with 18.0-μL Dnase free water and 2.5-μL CutSmart buffer. Then, the mixture was spun down for a few seconds and incubated at 37°C for 20 minutes. The PCR product was also sent for DNA sequencing for validation.

Electrophoresis
The 10- to 12-μL digested DNA was added with 1- to 2-μL BlueJuice Gel Loading buffer (Invitrogen, Waltham, MA, USA) and loaded into the 2.5% Agarose gel for *IL-1A* and 2% Agarose gel for *IL-1B*. Following that, the digested DNA was separated on the Agarose gel and stained with SYBR Safe DNA gel stain at 75 V for 90 minutes and 70 V for 60 minutes for *IL-1A* and *IL-1B*, respectively. The image on the Agarose gel was then visualised under ultraviolet light and captured using an image analyser i.e., Quantity One, 1-D Analysis Software (Bio-Rad Laboratories, Hercules, CA, USA).

Statistical analysis
The statistical calculation and evaluation were performed with IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). The data analysis was derived descriptively and the inferential statistics mainly used Pearson chi-square test, Fisher exact test and simple logistic regression. A *p* value of less than 0.05 is considered significant.

Ethical approval
The study protocol was approved by Human Research Ethics Committee of Universiti Sains Malaysia (Federalwide Assurance Registration No. 00007718; Institutional Review Board No. 00004494) and the written informed consent was gained from all participants.

RESULTS

From 138 participants, there were 61 males (44.2%) and 77 females (55.8%). The mean (standard deviation, SD) age at diagnosis was 46.6 (13.70) and 34.41 (12.37) years for CRSwNP and CRSsNP, respectively. Meanwhile, the mean (SD) age for cases and control was 40.52 (14.36) and 42.41 (12.26) years. Majority of the subjects was Malay in origin followed by Chinese, Indian, and others. Cigarette smoking was significantly associated with CRSwNP and CRSsNP patient (*p* < 0.001).
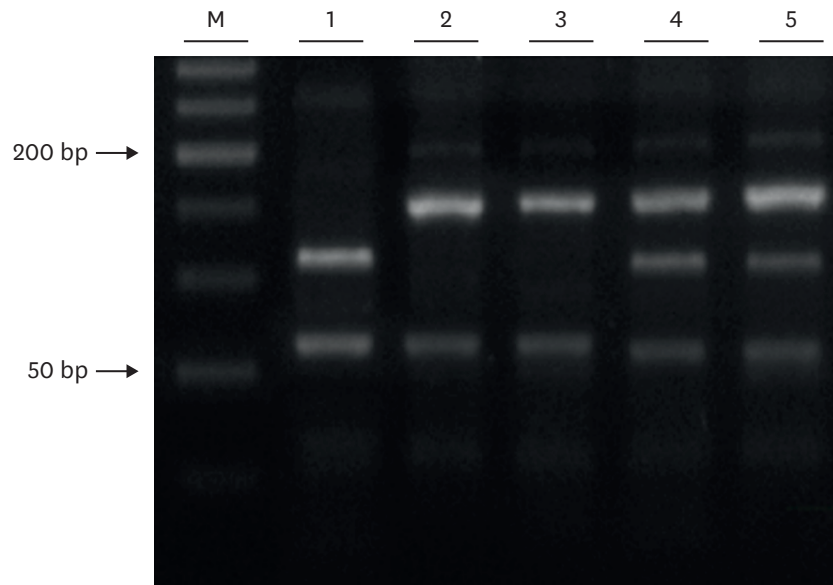
Fig. 1. A restriction fragment length polymorphism analysis of *IL-1A* (+4845G, +4845T) gene. Lane 1, homozygous wild (GG); lanes 4 and 5, heterozygous mutant (GT); lanes 2 and 3, homozygous mutant (TT); M, 50-bp DNA ladder. bp, base pair.

The SNPs for *IL-1A* (+4845G, +4845T) and *IL-1B* (−511C, −511T) were successfully genotyped. For *IL-1A* (+4845G, +4845T), homozygous wild-type (GG) expected to produce three fragments of 124 bp, 76 bp, and 29 bp. However, the 29 bp was too small to be captured in the 2.5% Agarose gel electrophoresis. Homozygous mutant-type (TT) produced 2 fragments of 153 bp and 76 bp, and therefore, heterozygous mutant-type (GT) was seen to yield 153 bp, 124 bp, 76 bp, and 29 bp fragments as shown in **Fig. 1**. On the other hand, the uncut fragment of 305 bp represented the homozygous wild-type (CC) for *IL-1B* (−511C, −511T). Heterozygous mutant-type (CT) yielded three fragments of 305 bp, 190 bp, and 115 bp, and homozygous mutant-type (TT) produced 2 fragments of 190 bp and 115 bp as shown in **Fig. 2**.

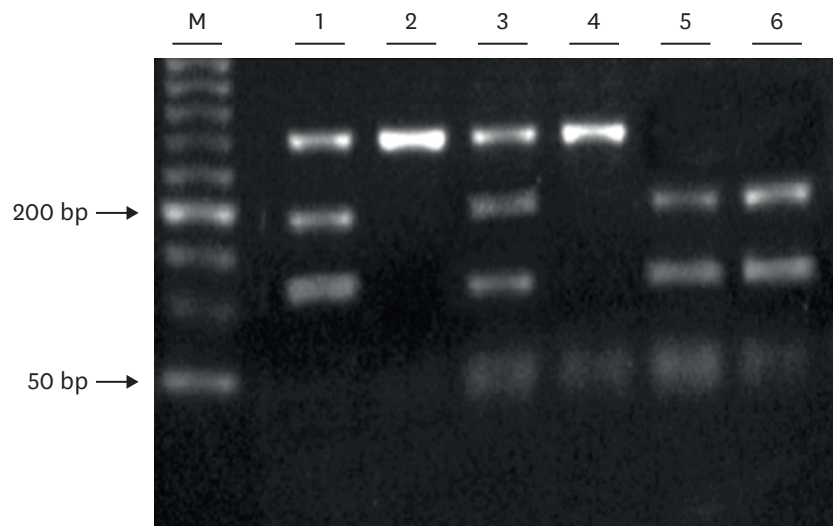**Fig. 2.** A restriction fragment length polymorphism analysis of *IL-1B* (−511C, −511T) gene. Lanes 2 and 4, homozygous wild (CC); lanes 1 and 3, heterozygous mutant (CT); lanes 5 and 6, homozygous mutant (TT); M, 50-bp DNA ladder. bp, base pair.

Table 1. Genotype distribution and allele frequencies of *IL-1A* (+4845G, +4845T) and *IL-1B* (−511C, −511T) genes in CRS participants (including CRSwNP and CRSsNP) and controls

Cytokine gene	CRSwNP	CRSsNP	Control	*p* value
IL-1A (+4845G, +4845T)				
Genotype				0.093
GG	5 (10.9)	9 (19.6)	3 (6.5)	
GT	22 (47.8)	24 (52.2)	18 (39.1)	
TT	19 (41.3)	13 (28.3)	25 (54.3)	
Allele				0.021*
G	35 (38.0)	42 (45.7)	24 (26.1)	
T	57 (62.0)	50 (54.3)	68 (73.9)	
IL-1B (−511C, −511T)				
Genotype				<0.001*
CC	8 (17.4)	20 (43.5)	27 (58.7)	
CT	24 (52.2)	17 (37.0)	19 (41.3)	
TT	14 (30.4)	9 (19.6)	0 (0.0)	
Allele				<0.001*
C	40 (43.5)	57 (62.0)	73 (79.3)	
T	52 (56.5)	35 (38.0)	19 (20.7)	

Values are presented as number (%).
IL, interleukin; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyp; CRSsNP, chronic rhinosinusitis without nasal polyp; GG, homozygous wild-type for *IL-1A* gene; GT, heterozygous mutant-type for *IL-1A* gene; TT, homozygous mutant-type for *IL-1A* or *IL-1B* gene; CC, homozygous wild-type for *IL-1B* gene; CT, heterozygous mutant-type for *IL-1B* gene; G, guanine; T, thymine; C, cytosine.
*$p < 0.05$, statistically significant difference.

Table 1 illustrates the genotype distributions and allele frequencies of both *IL-1A* and *IL-1B* in CRSwNP, CRSsNP, and controls. The GT genotype of *IL-1A* was common in patients with CRSwNP and CRSsNP but not amongst controls. Whereas, TT was a common genotype in controls. Thus, these findings contributed to significantly higher frequency of T allele ($p = 0.021$). However, there was no statistically significant differences found between *IL-1A* (+4845G, +4845T) genotype distributions against CRSwNP, CRSsNP, and controls ($p = 0.093$).

Indeed, our study showed a significant association of *IL-1B* (−511C, −511T) polymorphism with both CRSwNP and CRSsNP patients ($p < 0.001$). A slightly different trend of genotype frequencies was observed in *IL-1B* (−511C, −511T) polymorphism. The frequency of CC genotype of *IL-1B* was significantly higher in CRSsNP and controls ($p < 0.001$). However, in patients with CRSwNP, CT genotype was markedly increased in *IL-1B*. In terms of allele frequency, allele T was found to be highly associated with CRSwNP compared to CRSsNP and control groups ($p < 0.001$).

No significant association was found in all factors related to CRS, which includes asthma, atopy, allergy, aspirin sensitivity, and family history of NP with respective *p* values (all $p > 0.05$), as shown in **Table 2**.

Table 2. Association of other factors related to CRS with and without nasal polyp

Variable	CRSwNP (yes/no, n)	CRSsNP (yes/no, n)	Regression coefficient (b)	Crude OR (95% CI)	*p* value
Asthma	18/28	14/32	−0.39	0.68 (0.29–1.61)	0.382
Atopy	14/32	18/28	−0.39	0.68 (0.29–1.61)	0.382
Allergy	37/9	42/4	0.94	2.55 (0.73–8.99)	0.144
Aspirin sensitivity	1/45	1/45	0.00	1.00 (0.06–16.49)	>0.95
Family history of nasal polyp	5/41	2/44	0.99	2.68 (0.49–14.60)	0.254

CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyp; CRSsNP, chronic rhinosinusitis without nasal polyp; OR, odd ratio; CI, confidence interval.

DISCUSSION

This study demonstrated that there was a statistically significant association between *IL-1B* (−511C, −511T) polymorphism with both CRSwNP and CRSsNP patients ($p < 0.001$) which is consistent with a study by Erbek et al. [5] in a Turkish population. This proves that single nucleotide polymorphism (SNP) of *IL-1B* within the promoter region at locus −511 in chromosome 2 maybe one of the key players in the inflammatory cascade of CRSwNP as well as CRSsNP. However, the means by which this gene results in the clinical progression of the disease is unknown. The *IL-1B* (−511C, −511T) polymorphism may affect or alter the transcription of other cytokine genes involved in the disease process [21]. Perhaps further studies of this gene can be conducted in an even larger sample size to reduce the risk of random association between SNPs and CRS patients.

Our finding of CT genotype of *IL-1B* as a significantly common genotype ($p < 0.01$) in CRSwNP population is also similar to other studies [5, 12, 14]. However, studies by Cheng et al. [12] and Erbek et al. [5] showed that CT genotype as a common genotype in CRSsNP population. This may imply that CT genotype of *IL-1B* gene is an important genotype for development of both CRSwNP and CRSsNP in Asian population. In contrary, other studies [12, 15] also investigated the association of genetic polymorphism of *IL-1B* at position −511 and at different polymorphism site such as at exon 5 for *IL-1B* (+3953C, +3953T). However, no statistical difference was found between those genes and subjects tested. **Table 3** showed various studies performed investigating *IL-1A* and *IL-1B* polymorphism with nasal polyposis in different populations.

Even though our study did not find any association between *IL-1A* (+4845G, +4845T) genotype distributions against CRS patients and controls ($p = 0.093$), but the role of IL-1A gene family still cannot be ruled out as other studies [5, 6, 14] had shown significant association as summarised in **Table 3**. This leads to a possibility that variation exists between the ethnicity affecting frequency of many genetic alleles [16]. Besides that, this lack of association between *IL-1A* (+4845G, +4845T) gene polymorphism and CRSwNP or CRSsNP, maybe contributed by epigenetic factors such as environmental factor interacting within the genome and immunologic process modified by immunomodulator prescribed to the patient [10, 21]. For example, macrolides used in treatment of CRSwNP, may inhibit neutrophilic rather than eosinophilic activity and macrophage activation, and lower the IL-1B concentration [22].

Table 3. Various studies performed investigating *IL-1A* and *IL-1B* gene polymorphism with nasal polyposis in different populations

Study	Country	Study population	Common genotypes		Conclusion
			IL-1A (+4548G/T)	*IL-1B* (−511C/T)	
Karjalainen et al. [14]	Findland	NP in asthmatic adults	GG (NP); GT (without NP)	CT (NP); CC (without NP)	There was an association of *IL1A+4845* polymorphism with NP in asthmatic patients
Cheng et al. [12]	Taiwan	CRS patients	-	CT (CRSwNP and CRSsNP)	There was an association of *IL1RN* polymorphism in CRS patient
Erbek et al. [5]	Turkey	NP patients	GT (NP); GG (without NP)	CT (NP and without NP)	There was an association of *IL1A+4845*, *IL1B-511*, and *TNFα-238* to NP patients
Bernstein et al. [15]	USA	CRSwNP	-	-	There was an association of *TNF-α308* with CRSwNP patients but not to *IL-1β-511*
Mfuna Endam et al. [6]	Canada	CRSwNP and CRSsNP patients	-	-	Identified 3 potential new associations in *IL1A* polymorphism and severe CRS but not with *IL1B*

NP, nasal polyp; CRS, chronic rhinosinusitis; CRSwNP, CRS with nasal polyp; CRSsNP, CRS without nasal polyp; IL-1A, interleukin-1A; IL-1B, interleukin-1B; IL1RN, interleukin-1 receptor antagonist gene; TNF, tumour necrosis factor; GG, homozygous wild-type for *IL-1A* gene; GT, heterozygous mutant-type for *IL-1A* gene; CC, homozygous wild-type for *IL-1B* gene; CT, heterozygous mutant-type for *IL-1B* gene; G, guanine; T, thymine; C, cytosine; *IL-1A* (+4548G/T) equals to *IL1α+4845*; *IL-1B* (−511C/T) equals to *IL-1β−511*.

No significant association found in this study for the factors related to CRSwNP and CRSsNP patients with regards to asthma, atopy, allergy, aspirin sensitivity, and family history of nasal polyp (all $p > 0.05$). However, our demographic data revealed that there was an association of environmental factor such as smoking history with CRS patients ($p = 0.017$) which is consistent with other studies [2, 23].

There was a well-established association between aspirin sensitivity, asthma and CRSwNP termed "aspirin-exacerbated respiratory disease" or Samter's triad [24, 25]. Failure in obtaining association with aspirin sensitivity in the present study could be due to the low number of patients (only 2 patients out of total 138 subjects) who had consumed aspirin. This low incidence maybe due to an underestimation of aspirin sensitivity as the data was again based on patient's history and majority of our patients may have not taken aspirin before. Aspirin is commonly used as a prophylaxis for cardiovascular diseases worldwide. It was underutilised in Asian countries compared to Western population maybe due to overestimation of bleeding risks by the physicians [26].

The relationship of CRSwNP and positive family history of nasal polyp has been well established [1, 27, 28]. Nevertheless, an identical twin study showed that both siblings did not always develop nasal polyps and this discordance proposed the role of environmental factors that may affect disease expression [1, 29]. The lack of association of family history of nasal polyp and CRS in our study was obtained maybe contributed by underestimation of family history of nasal polyp. Some of our patients claimed that their family member had not seek any medical check-up as they were asymptomatic, thus assuming that their family member does not have any nasal polyp.

In terms of study limitation, the subjects were not homogenously distributed between the subgroups. The subjects should be equally matched for age, sex, and ethnicity to reduce the bias by the confounders. We attempted to reduce the environmental bias by matching the subjects geographically. In terms of sample size, the number of cases in our study (n = 92) is comparable to other studies (a total number of 35–179 cases) [5, 12, 14, 15]. This study might not represent the general population in Malaysia because the distribution of ethnic groups in Kelantan differs from other states of Malaysia. Therefore, a larger sample size and multicentre study would be more representative of CRS population in Malaysia.

In conclusion, this study indicates an association of *IL-1B* (−511C, −511T) polymorphism with CRSwNP and CRSsNP in our population, hence there is a possibility of *IL-1B* involvement in modulating pathogenesis of CRS. Therefore, it can be a potential new target for treatment of CRS. We hope that this finding added a significant value in contributing to understanding of genetics and pathogenesis of CRS in our population. Perhaps future research can improvise this study to use *IL-1B* as a genetic marker for disease susceptibility and risk stratification especially in patients with CRSwNP so that we can predict which patients are predisposed to recurrence of nasal polyp and may need revision nasal surgery.

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