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REVIEW ARTICLE

The role of IL-13 serum levels with its genetic polymorphism in the risk of developing chronic rhinosinusitis

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Abstract:

Background:Chronic rhinosinusitis (CRS) represents a prolonged inflammatory condition of both the nasal cavity and paranasal sinuses that extends more than 12 weeks without any sign of improvement. This condition affects work attendance along with productivity levels and quality of life detrimentally.

Objective: To find out whether IL-13 rs1800925 C/T-1055 genetic polymorphism and its serum levels have a risk value for CRS disease.

Methods: Three groups have been used as the basis for a case-control study. Thirty patients with a history of chronic rhinosinusitis with nasal polyps, thirty patients with a history of chronic rhinosinusitis without nasal polyps, and thirty healthy volunteers with no family history of CRS were included in the third group as control subjects. Blood samples were collected from each patient and the control group. To investigate the genetic polymorphism for IL-13 rs1800925 C/T-1055, two milliliters of blood were collected in an EDTA tube for complete DNA extraction. Three milliliters of blood were collected in a gel tube, after which the serum was separated by centrifugation and used for the ELISA test to measure the amount of IL-13 in the serum.

Results: This study revealed no statistical differences between patients affected by CRS across different sex groups and age ranges. The CT genotype frequency of IL13 showed a significant increase in patients with nasal polyps compared to patients without nasal polyps ($p = 0.007$). Serum IL-13 levels were found to be significantly higher in the CRS group than in the control group, with the highest levels seen in the nasal polyps group ($p=0.042$).

Conclusion: present data indicate a relationship between the IL-13 rs1800925 C/T-1055 SNP and the development of chronic rhinosinusitis in Iraqi patients. Because such a genotype was found to affect the IL-13 concentration in the serum of those patients, which makes the condition more severe.

Keywords: chronic rhinosinusitis, chronic rhinosinusitis with nasal polyp, IL-13, IL-13 serum levels.

Introduction

Chronic rhinosinusitis (CRS) represents a heterogeneous multifactorial condition that involves persistent inflammation within the nasal and paranasal sinus mucosal tissue while displaying at least two primary symptoms, which include nasal discharge or nasal obstruction with loss of smell in addition to facial pain or pressure symptoms that last for at least 12 weeks (1). This condition affects approximately 12% of the global population (1), which has substantial impacts on both workplace productivity levels and life quality as well as employee work attendance. As a result, surgical intervention takes place more than one million times annually across the world (2). CRS has been divided into two distinct phenotypic groups: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP), depending on whether patients present with polyps or not (3). CRS exhibits diverse pathological mechanisms throughout its development process (2, 4–6). Interleukin (IL-) 13 functions as a pleiotropic cytokine, which contributes to polyp development. The release of IL-13 activates eosinophils and leads to inflammatory cell recruitment along with monocyte differentiation into macrophages (2, 7, 8). IL-13 induces hyperplasia of goblet cells in epithelial cells and smooth muscle cell proliferation (9, 10). The human IL-13 gene resides on chromosome 5 at position 5q23–31 (11). To the best of our knowledge, no research has examined the connection between IL-13 SNP and chronic rhinosinusitis, while several have examined its function in asthma, so the purpose of this study was to assess how IL-13 gene polymorphism contributes to chronic rhinosinusitis and the reasons why patients do not improve with treatment. Additionally, show whether its serum level may contribute to the pathophysiology of the disease.

Materials and Methods

Patient and Sample Collection

Three groups have been used as the basis for a case-control

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study. Thirty patients in the first group had previously been diagnosed with chronic rhinosinusitis with nasal polyps, and thirty patients in the second group had previously been diagnosed with chronic rhinosinusitis without nasal polyps. This study included all cases that were seen at the Al-Diwaniyah Teaching Hospital's consultant clinic for otorhinolaryngology between August 2024 and October 2024 under the care of an ear, nose, and throat physician, and data were collected from each patient. Thirty healthy volunteers without a family history of chronic rhinosinusitis were included in the third group. A sterile syringe was used to draw approximately 5 mL of venous blood from each group in an aseptic condition. Two tubes are used to collect blood samples. To investigate the genetic polymorphism for IL-13 rs1800925 C/T-1055, about 2 ml of blood was collected in an EDTA tube for complete DNA extraction, and 3 ml of blood was collected in a gel tube and allowed to clot before the serum was separated by centrifugation at 1500 rpm for 5 minutes. The serum was collected in an Eppendorf tube and kept at -20°C for the ELISA test, which measures the amount of IL-13 in the serum.

Serological test

ELISA Kit for IL-13: The interleukin-13 serum concentration was measured through a double-antibody sandwich enzyme-linked immunosorbent assay protocol from Elabscience. O.D. readings at a wavelength of 450 nm revealed interleukin 13 levels through standard curve comparison.

Genomic DNA extraction: The gSYAN DNA extraction kit (Frozen Blood) from Geneaid, USA, was used to extract the genomic DNA from the blood samples. It was completed according to the guidelines in the instruction manual. To determine the purity of the DNA, absorbance at 260 and 280 nm was measured using a Nano-drop spectrophotometer (THERMO, USA).

T-ARMS-PCR: The Tetra-Amplification-Refractory Mutation System Polymerase Chain Reaction technique (T-ARMS-PCR) assay was used to genotype patients and the control group in order to detect and identify the IL-13 rs1800925 C/T-1055 gene polymorphism. The steps used in this procedure were as follows:

Utilizing the GoTaq® Green Master Mix Kit, the T-ARMS-PCR master mix was created in accordance with the manufacturing company's instructions, which are listed in Table 1.

Table 1: PCR Master Mix

T-ARMS-PCR Master mix	Volume
DNA template	5µl
Forward inner primer (wild allele) (10pmol)	1µl
Reverse inner primer (mutant allele) (10pmol)	1µl
Forward outer primer (10pmol)	1µl
Reverse outer primer (10pmol)	1µl
G2 Green Master Mix	12.5µl
Nuclease free water	3.5µl
Total volume	25µl

Primers: This study used the NCBI-SNP database as well as (PRIMER1: primer design for tetra-primer ARMS-PCR) to create gene polymorphism Tetra-ARMS-PCR Primers. These primers were provided by (ScientificReseracher. Co. Ltd. Iraq) as the following table:

Table 2: The Tetra-ARMS-PCR Primers for rs1800925 C/T-1055 gene polymorphisms with their sequence and amplicon size

T-ARMS-PCR Primer	Sequence (5'-3')	Product size
Forward inner primer (C allele):	TTTCTGGAGGACTTCTAGGAACAC	229bp
Reverse inner primer (T allele)	TTTCCTGCTCTTCCCGCA	287bp
Forward outer primer	GTTCCCTGTGGGAAGAGAGG	474bp
Reverse outer primer	CTGGCAGCCTTAGTCCAGGT	

The PCR master mix components stated above were then transferred to an Exispin vortex centrifuge and spun for three minutes at 3000 rpm. It was then put inside a BioRad PCR thermocycler (USA). And the condition of PCR mentioned in the Table:3.

Table 3: T-ARMS-PCR Thermocycling condition for IL-13 rs1800925 C/T-1055 gene detection

PCR step	Temp.	Time	repeat
Initial denaturation	95°C	5min.	1
Denaturation	95°C	30 sec.	35cycle
Annealing	62°C	30 sec.	
Extension	72°C	30 sec.	
Final extension	72°C	5min	1
Hold	4°C	Forever	-

Evaluation of PCR results: The hexon gene PCR amplification products were assessed using migration on agarose gel electrophoresis. Initially, 2% agarose gel was made using 1X TBE. It was then dissolved in a water bath at 100°C for 15 minutes and allowed to cool to 50°C. Next, 3 µL of ethidium bromide dye was added to the agarose gel solution. The tray was filled with the agarose gel solution once the comb was positioned correctly. The comb was gently taken out of the tray after it had been set for 15 minutes at room temperature. After being filled with 1X TBE buffer, the gel tray was placed inside the electrophoresis chamber. Each comb received 10 µL of the PCR product, and the first well received 3 µL of the 100 bp ladder. For one hour, the electric current was run at 80 milliamperes and 100 volts. The T-ARMS-PCR products were visualized using a UV transilluminator.

Statistical analysis of data: The analysis of data statistics involved the use of Statistical Package for Social Sciences (SPSS) version 16 and Microsoft Office Excel software 2010 to examine raw data and present findings. The analysis included qualitative (categorical) data presentation as numbers and percentages, while quantitative (numeric) data required evaluation for normality distribution through the Kolmogorov-Smirnov test to determine appropriate expression as mean. The statistical analysis employed p-values lesser or equivalent to 0.05 for determining significance.

Results:

Demographic characteristics of the patient group and control group

The patients' group and control group demographic data are presented in Table 4. The participants in each group had an average age of 40.93 ±14.01 years, 39.90 ±10.40 years, and 42.70 ±20.34 years for the nasal polyp group, the without nasal polyp group, and the control group, respectively. Comparison of age data showed no statistically significant variation (p = 0.151). Male and female proportions in the study group were not significantly different, with 13 (43.3%) and 17 (56.7%) versus 17 (56.7%) and 13 (43.3%) versus 14 (46.7%) and 16 (53.3%) for the nasal polyp group, the without nasal polyp group, and the control group, respectively (p = 0.561).

Table 4: Demographic characteristics of patients group and control group

Characteristic	Nasal polyp group n = 30	Without nasal polyp n = 30	Control group n = 30	p
Age (Years)				
Mean ±SD	40.93 ±14.01	39.90 ±10.40	42.70 ±20.34	0.151 O NS
Range	14 -64	10 -60	13 -72	
Sex				
Male	13 (43.3 %)	17 (56.7 %)	14 (46.7 %)	0.561 C NS
Female	17 (56.7 %)	13 (43.3 %)	16 (53.3 %)	

SD: standard deviation; n: number of cases; O: one way ANOVA; C: chi-square test; NS: not significant

Such case-control studies need specific results that show matching between age and sex to prevent these variables from shaping biases in their studied parameters.

Comparison of genotypes of IL-13 CT and allele frequencies between the patient group and the control group

Table (6) presents findings regarding IL-13 CT genotypes as well as allele frequencies between nasal polyp patients and control participants. There were no significant differences in any of the CC, CT, or TT genotype frequencies between groups (p > 0.05). The groups did not differ significantly in terms of allele frequency distributions (p = 0.540).

Table (6): Comparison of IL-13 CT genotypes and allele frequencies between Nasal polyp group and control group

Characteristic	Nasal polyp group	Control group	p	OR	95% CI
IL-13 CT genotype					
CC	15 (50.0 %)	17 (56.7 %)	0.605 C NS	0.76	0.28 -2.11
CT	12 (40.0 %)	11 (36.7 %)	0.791 C NS	1.15	0.41 -3.26
TT	3 (10.0 %)	2 (6.7 %)	0.640 C NS	1.56	0.24 -10.05
Allele					
C	42 (70.0 %)	45 (75.0 %)	0.540 C NS	0.78	0.35 -1.74
T	18 (30.0 %)	15 (25.0 %)		1.29	0.58 -2.87

n: number of cases; C: chi-square test; NS: not significant; OR: odds ratio; CI: confidence interval

Table (7) shows the IL-13/CT genotype comparison with allele frequencies between subjects with no nasal polyps and control participants. The genotypes CC and TT showed no statistical differences across the No nasal polyp group and the control group (p > 0.05), while the CT genotype occurred at a lower rate in the No nasal polyp group when compared to the control (p = 0.015). Risk analysis conducted a statistical assessment producing an odds ratio value of 0.19, while its calculated confidence interval ranged from 0.05 to 0.78. Statistical analysis showed no significant variation existed between the allele frequencies of the no nasal polyp group and the control group (p = 0.171). Figure (1) demonstrates the results of T-ARMS-PCR analysis for detecting IL-13 rs1800925 C/T-1055 gene polymorphisms on agarose gel electrophoresis.

Table (7): Comparison of IL-13/CT genotypes and allele frequencies between No nasal polyp group and control group

Characteristic	No nasal polyp	Control group	p	OR	95% CI
IL-13 CT genotype					
CC	24 (80.0 %)	17 (56.7 %)	0.052 C NS	3.06	0.97 -9.66
CT	3 (10.0 %)	11 (36.7 %)	0.015 C *	0.19	0.05 -0.78
TT	3 (10.0 %)	2 (6.7 %)	0.640 C NS	1.56	0.24 -10.05
Allele					
C	51 (85.0 %)	45 (75.0 %)	0.171 C NS	1.89	0.75 -4.73
T	9 (15.0 %)	15 (25.0 %)		0.53	0.21 -1.33

n: number of cases; C: chi-square test; NS: not significant; OR: odds ratio; CI: confidence interval; *: significant at p ≤ 0.05

Table (8) presents data on IL-13/CT genotypes and allele frequencies between participants with nasal polyps and patients without nasal polyps. Results indicated that the CC genotype occurred less frequently in nasal polyp patients when compared to non-nasal patients (p = 0.015) with an odds ratio of 0.25 (confidence interval of 0.08-0.79). CT genotypes occurred more frequently among patients with nasal polyps compared to those without nasal polyps (p = 0.007) and demonstrated an odds ratio of 6.00 (1.48-24.30). Results revealed TT genotypes displayed no significant difference (p = 1.000).

Table (8): Comparison of IL-13/CT genotypes and allele frequencies between nasal polyp group and No nasal polyp group

Characteristic	Nasal polyp group	No nasal polyp	p	OR	95% CI
IL-13 CT genotype					
CC	15 (50.0 %)	24 (80.0 %)	0.015 C *	0.25	0.08 -0.79
CT	12 (40.0 %)	3 (10.0 %)	0.007 C **	6.00	1.48 -24.30
TT	3 (10.0 %)	3 (10.0 %)	1.000 C NS	1.00	0.19 -5.40
Allele					
C	42 (70.0 %)	51 (85.0 %)	0.049 C *	0.41	0.17 -1.01
T	18 (30.0 %)	9 (15.0 %)		2.43	0.99 -5.96

n: number of cases; C: chi-square test; NS: not significant; OR: odds ratio; CI: confidence interval; *: significant at p ≤ 0.05; **: significant at p ≤ 0.01

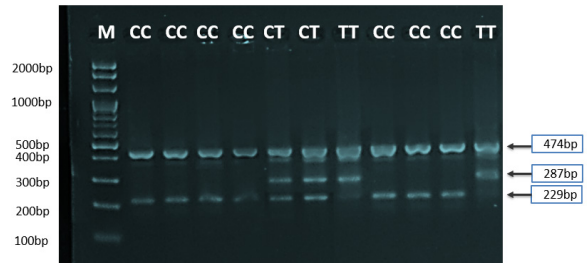

Figure (1): Agarose gel electrophoresis image that showed the T-ARMS-PCR product analysis of IL-13 rs1800925 C/T-1055 gene polymorphisms. Where M: marker (2000-100bp). The lane (CC) wild type homozygote was showed C allele at 229bp T-ARMS-PCR product. The lane (TT) mutant type homozygote was showed T allele at 287bp T-ARMS-PCR product, whereas the (CT) heterozygote were showed as both C and T allele at 229bp and 287bp T-ARMS-PCR product. The outer internal control was observed at 474bp T-ARMS-PCR product.

Comparison of mean IL-13 serum levels between patients' group and control group

Table (9) displays the mean serum IL-13 measurements which compare between patients and control groups. Patients showed higher IL-13 concentrations than controls at significantly different levels with nasal polyp patients having highest IL-13 followed by no nasal polyp patients and control group.

For that reason, ROC curve analysis assessed the diagnostic capability of this marker as presented in Figures (2) and Table (10).

Table (9): Comparison of mean IL-13 serum levels between patients group and control group

Characteristic	Nasal polyp group n = 30	No nasal polyp n = 30	Control group n = 30	p
IL-13 (pg/ml)				
Mean ±SD	80.44 ±15.79 A	72.87 ±28.48 B	65.36 ±22.15 C	0.042 O *
Range	40.01 -130.8	17.7 -129.5	18.34 -102.36	

SD: standard deviation; n: number of cases; I: independent samples t-test; *: significant at p ≤ 0.05; A, B and C letters were used to indicate levels of significance after performing post hoc LSD test

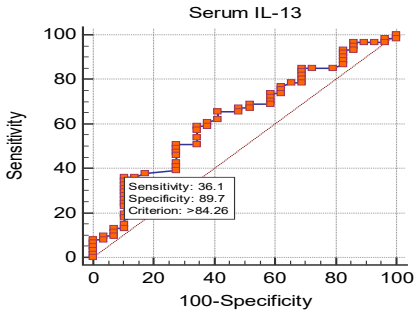

Figure (2): Receiver operating characteristic (ROC) curve performed to find the cutoff value of serum IL-13

Table (10): The results of ROC curves for serum IL-13

Characteristic	Serum IL-13
Cutoff value	> 84.26 pg/ml
AUC	0.632
95 % CI	0.523 to 0.731
p-value	0.035 *
Sensitivity %	36.1
Specificity %	89.7
Accuracy %	63.2

AUC: area under curve; CI: confidence interval; *: significant at p ≤ 0.05

Discussion:

The patient-based sample design in this current study employed 30 subjects for each case group, affecting the gender balance among affected patients. Research in Germany revealed CRS prevalence did not differ according to patients' ages in their study population (12). Such a study's findings correspond to the present study's results. The mucociliary function of people transforms with aging processes. A study done by Ho et al. shows that older age groups experience reduced ciliary beat rates together with worsened core microtubule abnormalities

in cilia that might explain age-related increasing rates of this illness (13).

This study has established for the 1st time a promoter polymorphism of IL-13 at -1055C>T in patients with chronic rhinosinusitis. The CT genotype frequencies with their haplotypes demonstrated significant differences between patients who had nasal polyps and those who did not develop polyps, which suggests the CT genotype functions as a risk factor for developing nasal polyps. Eosinophilic infiltration might occur because of regulatory elements arising from these polymorphisms. However, a study based on a larger cohort needs to be conducted to verify these findings.

IL-13 controls allergic inflammatory activities by managing inflammatory cell activation and homing mechanisms and by attracting T cells and eosinophils into the airway. The IL-13 released from mast cells and eosinophils leads to IgE production in cultured B cells. A study demonstrates that variations in the IL-13 gene lead to higher total IgE serum levels and elevated eosinophil numbers together with suspected asthma exacerbation links (17).

Evidence suggests a connection between this site and the severity of asthma and airway hyperresponsiveness. (AHR) (Marsh et al., 1994; Noguchi et al., 1997; Palmer et al., 1998). A mutation in the IL-13 promoter region known as rs1800925 is referred to by multiple names, including -1112, -1111, and -1055 C/T (17–19), which causes a C to T base change that takes place in the 5' promoter region (20). The expression of both IL-13 mRNA and protein increases due to the IL-13 rs1800925 SNP leading to cytokine release while activating the JAK/STAT6 pathway, which induces gene expression and messenger RNA conformation, thus causing allergic asthma (21).

Only a limited number of studies examine the serum levels of IL-13 in CRS. Nabavi et al. revealed that patients with CRSwNP exhibited increased IL-13 serum levels compared to control participants (22). A study demonstrated that individuals with CRS either presented NPs or did not demonstrate enhanced IL-13 gene mRNA expression in their tissue samples in comparison to control participants. The highest levels of expression occurred among patients who had CRSwNP (23). Previous studies have shown that IL-13 mRNA expression rises in the NP (24, 25). These findings match the results obtained in the present study.

Conclusion:

The current study demonstrates that the IL-13 rs1800925 C/T-1055 SNP plays a role in elevating the chance of developing chronic rhinosinusitis for Iraqi patients. Additionally, IL-13 serum levels respond to such allelic genotypes in patients with chronic rhinosinusitis, and this, in turn, affects the severity of their illness.

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