## Original article

# IL 13rs20541 single nucleotide polymorphism and serum IL -13 level in children with bronchial asthma

***Background:*** *Bronchial asthma is a common respiratory illness affecting adult and pediatric populations. Interleukin (IL)-13 is a central key mediator of allergic inflammation, and it plays a pivotal role in the pathogenesis of asthma. Several studies revealed that genetic variants of IL-13 promoter rs1800925 allele play a role in asthma severity. We sought to investigate the role of IL-13 rs20541 single nucleotide polymorphism (SNP) and serum IL -13 level in relation to asthma severity in a group of asthmatic children.* ***Methods****: This controlled cross-sectional study included 80 participants: 40 apparently healthy controls and 40 asthmatic children, subdivided into three groups: mild (n=12), moderate (n=18 cases), and severe (n=10), recruited from Pulmonology Unit, Children's Hospital, Ain shams university. Characterization of IL-13 rs20541 SNP was achieved by TaqMan real-time PCR. Serum IL-13 concentration was measured using a commercial sandwich ELISA assay.* ***Results****: The dominant genotype as regards IL-13 rs20541 SNP among patients and controls was GA (60% and 92.5%, respectively). G and A allele frequencies between patients and controls differed significantly (p =0.002) as the dominant allele in the control group was G allele (70.0%), versus the A allele in the patients' group (53.8%). Patients had statistically significantly higher levels of IL-13 compared to controls (median= 45 pg/ml versus 4 pg/ml; p<0.001) Serum IL-13 correlated positively with IgE levels and was able to discriminate between patients with severe asthma and those with mild to moderate asthma at cut off value of >83 pg/ml (sensitivity 90%, specificity 90%, positive predictive value 96.4% and negative predictive value 75%).* ***Conclusion****: IL-13 rs20541 SNP polymorphism is associated with asthma in Egyptian children, while serum IL-13 is linked to the severity of asthma.*

Key words: IL 13rs20541, Serum IL -13, children, bronchial asthma

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## INTRODUCTION

Bronchial asthma is one of the commonest respiratory illnesses that affect both adult and pediatric populations.[1] Several genetic and environmental factors play pivotal roles in its development and progression.[2] Asthma immunopathogenesis includes a lot of humoral and cellular components.[3] Thus, studying the genetic variability of these components will contribute to the overall understanding of the disease.

Interleukin-13 (IL-13) is a central mediator of the allergic inflammation and plays an essential role in the pathogenesis of asthma.[4] Its main producer is activated T helper cells and, to a lesser extent, eosinophils, basophils, mast cells, and natural killer T cells.[5] In the airways, IL-13 promotes the migration of inflammatory cells, mucus production by epithelial cells, subepithelial fibrosis, and airway hyperresponsiveness. It also switches B cells to produce immunoglobulin E (IgE).[6]

Recently, an accumulated body of evidence suggests a link between several IL-13 gene polymorphisms and the heterogeneity in bronchial asthma severity and response to medications.[6] Many studies have characterized two single nucleotide polymorphisms (SNPs) in IL-13; a promoter SNP (-1111, rs1800925) and a coding SNP in exon 4 (Arg130Gln, rs20541). However, their exact role in bronchial asthma needs more elucidation, especially in the presence of conflicting data from different ethnicities.[1,4,5]

In this study, we investigated the role of IL-13 rs20541 SNP and serum IL -13 level in asthma and its severity among a group of asthmatic children.

## METHODS

We conducted a controlled cross-sectional study that comprised 80 participants divided into two

groups: patients and controls. The patients' group included 40 asthmatic children (23 males and 17 females) who were recruited from the pediatric chest clinic, children's hospital, Ain Shams University (ASU), Egypt, from January 2021 to June 2021. Their ages ranged from 3-14 years, with a mean age of 7.75 ± 3.06 years.

The control group comprised 40 apparently healthy children (20 males and 20 females) with a mean age of 7.43+2.44 years. They had no history of any allergic diseases.

Informed consent was obtained from the legal guardian of each patient and control before participation. The study was conducted according to the international guidelines of Strengthening the Reporting of Observational Studies in Epidemiology; STROBE.[7] The procedures applied in this study were approved by the Ethics Committee of Human Experimentation of ASU (FMASU R 109/2021) and are in accordance with the Helsinki Declaration of 1975 developed by the World Medical Association.[8]

Asthma diagnosis was applied according to the criteria approved by the global initiative for asthma.[9] Severity was assessed retrospectively from the level of treatment required to control symptoms. Accordingly, Patients were further subdivided into three groups: mild persistent (n=12), moderate persistent (n=18) and severe persistent (n=10) asthma. Patients with coexisting respiratory illnesses, acute infections, chronic inflammatory conditions, malignancies or who were on systemic immunosuppressive regimens were excluded from the study.

All patients and controls were subjected to full history taking laying stress on demographic data, other forms of atopy and controller medications. Full clinical examination was done.

Serum total IgE levels and complete blood count were collected from patient's medical records using a standardized data collection form.

***Laboratory workup***

Blood samples (2-3 mls) were collected from each participant by peripheral venipuncture under complete aseptic conditions, in two separate tubes: serum separator tubes and tubes containing EDTA. Samples were stored at -20ºC until further used.

*1. Genotyping of IL-13 rs20541 SNP:*

DNA was extracted from anticoagulated samples using commercial DNA extraction kit [Thermo Scientific™ Gene JET Whole Blood Genomic DNA Purification Mini Kit (Thermo Scientific, USA)], according to the manufacturer's instructions.

Characterization of the IL-13 rs20541 SNP, located on exon 4, was achieved by TaqMan (Applied Biosystems, USA) real time polymerase chain reaction (PCR) according to manufacturer's instructions. Briefly, the assay consisted of two specific primers (50-GG GCTCAAGGGCTCCTAACT-30; reverse primer, 50 -TCCCGCCTACCCAAGACA TT-30) and two TaqMan minor groove binder probes with non-fluorescent quenchers. One probe was labeled with VIC dye and the other was labeled with FAM dye to detect the two alleles sequence. TaqMan Genotyping Master Mix (Applied Biosystems, USA) was used in the reaction. The cycling conditions were set as previously described.[3] IL-13 rs20541 single nucleotide polymorphism (SNP) analysis and allelic discrimination were automatically obtained from Rotor-Gene Q software version 2.3.3.5 (Qiagen, Germany) and interpreted according to Liu et al.[3]

*2. Measuring serum IL-13:*

Serum IL-13 concentration was measured using a commercial sandwich Enzyme Linked Immuno-Sorbent assay (ELISA) (Bioassay Technology Laboratory, England/China, Cat. No: E0098Hu). The procedure was performed guided by the manufacturer's instructions. Results were read and interpreted using (Digital and Analogue System Plate Reader, Roma, Italy). With each assay a standard curve was plotted. The concentrations of IL-13 in samples were measured in pg/ml.

**Statistical analysis**

The sample size was calculated using PASS15 [10,11] program based on previous study.[3] Setting power at 80% and alpha error at 0.05, it was estimated that sample size of 20 children per group can detect a difference between the groups regarding IL-13 level with effect size of 0.4. Case to control ratio was 1:1. Qualitative variables were expressed as number (n) and percentage (%), quantitative variables were expressed as mean±SD (parametric data) and median (IQR) (non-parametric data).

The analytical statistics used included Chi-square test for comparison between qualitative variables, independent t-test (parametric), Mann-Whitney test (non-parametric) for comparison between 2 groups, Spearman's correlation coefficient (r) test for correlation between quantitative variables; One Way analysis of variance (ANOVA) and Kruskal-Wallis test were used when comparing more than 2 groups. Receiver-operating characteristic (ROC) curve analysis was used to examine the performance of IL-13 in discrimination between patients with

severe asthma and those with mild to moderate asthma. The confidence interval was set at 95% and the margin of error accepted was set at 5%, so p-value <0.05 was considered significant.

Statistical analysis was done by IBM SPSS (Statistical Package for the Social Sciences) version 26.0 (IBM© Corp., Armonk, NY)

## RESULTS

Relevant demographic, clinical and laboratory characteristics of participants in the patients' group are presented in table (1).

Comparing patients with different grades of asthma severity revealed statistically significant difference as regards age (*p=0.025*) and level of control *(p<0.001)*, where younger ages and uncontrolled asthma contributed to more severe course. Similarly, higher IgE (*p=0.035*), and IL-13 *(p<0.001)* levels were found in patients with severe asthma (table 1).

The data shows that patients had statistically significant higher levels of IL-13 as compared to controls *(p<0.001)* (table 2). Also, serum IL-13 correlated positively with IgE levels (figure 1) and was able to discriminate between patient with severe asthma and those with mild to moderate asthma at cut off value of >83 pg/ml (sensitivity 90%, specificity 90%, positive predictive value 96.4% and negative predictive value 75%) (figure 2).

Genotypic characterization of IL-13 rs20541 SNP showed that the dominant genotype among patients and controls was GA (60% and 92.5%, respectively) (table 2). The frequencies of alleles between patients and controls were significantly different *(p = 0.002)*, where the dominant allele in the control group was the G allele (70.0%) while the A allele was the dominant one in the patients' group (53.8%) (table 2).

On the other hand, IL-13 rs20541 gene polymorphism didn't show significant variation with any of the studied parameters among patients' group (table 3).

**Table 1.** Demographic, clinical and laboratory characteristics of patients with bronchial asthma (n=40)

| Variables | | All patients | Severity of asthma | | | Test value | P- value |
|---|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | | |
| | | n=40 | n= 12 | n= 18 | n= 10 | | |
| Age | Mean±SD | 7.75 ± 3.06 | 9.67 ± 3.26 | 7.17 ± 2.68 | 6.50 ± 2.59 | 4.064• | 0.025 |
| | Range (years) | 3 – 14 | 4 – 14 | 3 – 13 | 3 – 12 | | |
| Sex | Female | 17 (42.5%) | 6 (50.0%) | 6 (33.3%) | 5 (50.0%) | 1.125* | 0.570 |
| | Male | 23 (57.5%) | 6 (50.0%) | 12 (66.7%) | 5 (50.0%) | | |
| Level of control | Controlled | 23 (57.5%) | 11 (91.7%) | 12 (66.7%) | 0 (0.0%) | 19.881* | 0.000 |
| | Uncontrolled | 17 (42.5%) | 1 (8.3%) | 6 (33.3%) | 10 (100.0%) | | |
| Allergic rhinitis | No | 15 (41.7%) | 7 (63.6%) | 6 (37.5%) | 2 (22.2%) | 3.699* | 0.157 |
| | Yes | 21 (58.3%) | 4 (36.4%) | 10 (62.5%) | 7 (77.8%) | | |
| Total Ig E (IU/ml) | Median (IQR) | 98 (30 –750) | 36 (5 – 90) | 99 (30 – 556) | 750 (187 – 1000) | 6.709≠ | 0.035 |
| | Range | 5-1200 | 5 – 700 | 5 – 1200 | 10 – 1000 | | |
| TLC | Mean±SD | 10.43 ± 2.63 | 9.97 ± 2.70 | 11.01 ± 2.79 | 9.98 ± 2.35 | 0.634 | 0.537 |
| | Range | 6 – 16 | 6.1 – 14.6 | 6.1 – 16 | 7 – 14 | | |
| IL-13 rs20541 | GA<br>GG<br>AA | 37 (92.5%)<br>0 (0%)<br>3 (7.5%) | 10 (83.3%)<br><br>2 (16.7%) | 17 (94.4%)<br><br>1 (5.6%) | 10 (100.0%)<br><br>0 (0.0%) | 2.362* | 0.307 |
| | G | 37 (46.3%) | 10 (41.7%) | 17 (47.2%) | 10 (50.0%) | 0.330* | 0.848 |
| | A | 43 (53.8%) | 14 (58.3%) | 19 (52.8%) | 10 (50.0%) | | |
| IL-13 (pg/ml) | Median (IQR) | 45 (23.5 – 90) | 20 (17.5 – 24.5) | 45 (30 – 80) | 131.5 (90 – 180) | 25.904≠ | 0.000 |
| | Range | 13 – 200 | 13 – 70 | 20 – 120 | 70 – 200 | | |

Categorical variables are presented as either counts and percentages. continuous variables are presented as mean and standard deviation or median and interquartile range (IQR)

:*Chi-square test; •: One Way ANOVA test; ≠: Kruakal-Wallis test

IgE, Immunoglobulin E; IL-13, Interleukin 13; SD, standard deviation; TLC, total leukocytic count

**Table 2.** Comparison between patients and controls as regards IL-13 and IL-13 gene polymorphism (rs20541)

| | | Control group n= 40 | Patients group n= 40 | Test value | P-value |
|---|---|---|---|---|---|
| **IL-13 rs20541** | GG | 16(40.0%) | 0 (0.0%) | 21.770* | 0.000 |
| | GA | 24(60.0%) | 37 (92.5%) | | |
| | AA | 0 (0.0%) | 3 (7.5%) | | |
| | G | 56 (70.0%) | 37 (46.3%) | 9.270* | 0.002 |
| | A | 24 (30.0%) | 43 (53.8%) | | |
| **IL-13** (pg/ml) | Median (IQR) | 4 (3 – 5) | 45 (23.5 – 90) | -7.721≠ | 0.000 |
| | Range | 2 – 6 | 13 – 200 | | |

*: Chi-square test; ≠: Mann-Whitney test
IgE, Immunoglobulin E; IL-13, Interleukin 13, IQR; interquartile range

**Table 3.** Relation between IL-13 rs20541 gene polymorphism and different patients' parameters

| | | IL-13 rs20541 | | Test value | P-value |
|---|---|---|---|---|---|
| | | GA | AA | | |
| | | No.= 37 | No. 3 | | |
| Age | Mean±SD | 7.59 ± 2.81 | 9.67 ± 5.86 | -1.132• | 0.265 |
| | Range | 3 – 13 | 3 – 14 | | |
| Sex | Female | 16 (43.2%) | 1 (33.3%) | 0.112* | 0.738 |
| | Male | 21 (56.8%) | 2 (66.7%) | | |
| Severity of asthma | Control | 0 (0.0%) | 0 (0.0%) | 2.362* | 0.307 |
| | Mild | 10 (27.0%) | 2 (66.7%) | | |
| | Moderate | 17 (45.9%) | 1 (33.3%) | | |
| | Severe | 10 (27.0%) | 0 (0.0%) | | |
| Level of control | Controlled | 20 (54.1%) | 3 (100.0%) | 2.397* | 0.122 |
| | Uncontrolled | 17 (45.9%) | 0 (0.0%) | | |
| TLC | Mean±SD | 10.34 ± 2.73 | 11.40 ± 0.26 | -0.665• | 0.511 |
| | Range | 6.1 – 16 | 11.2 – 11.7 | | |
| Total Ig E(IU/ml | Median (IQR) | 97 (30 – 756) | 286 (5 – 350) | -0.148≠ | 0.883 |
| | Range | 5 – 1200 | 5 – 350 | | |
| Allergic rhinitis | No | 13 (39.4%) | 2 (66.7%) | 0.842* | 0.359 |
| | Yes | 20 (60.6%) | 1 (33.3%) | | |
| IL-13 | Median (IQR) | 50 (25 – 90) | 20 (20 – 25) | -1.800≠ | 0.072 |
| | Range | 13 – 200 | 20 – 25 | | |

Categorical variables are presented as either counts and percentages. continuous variables are presented as mean and standard deviation or median and interquartile range (IQR)
:*Chi-square test; •: Independent t-test; ≠: Mann-Whitney test
IgE, Immunoglobulin E; IL-13, Interleukin 13; SD, standard deviation; TLC, total leukocytic count

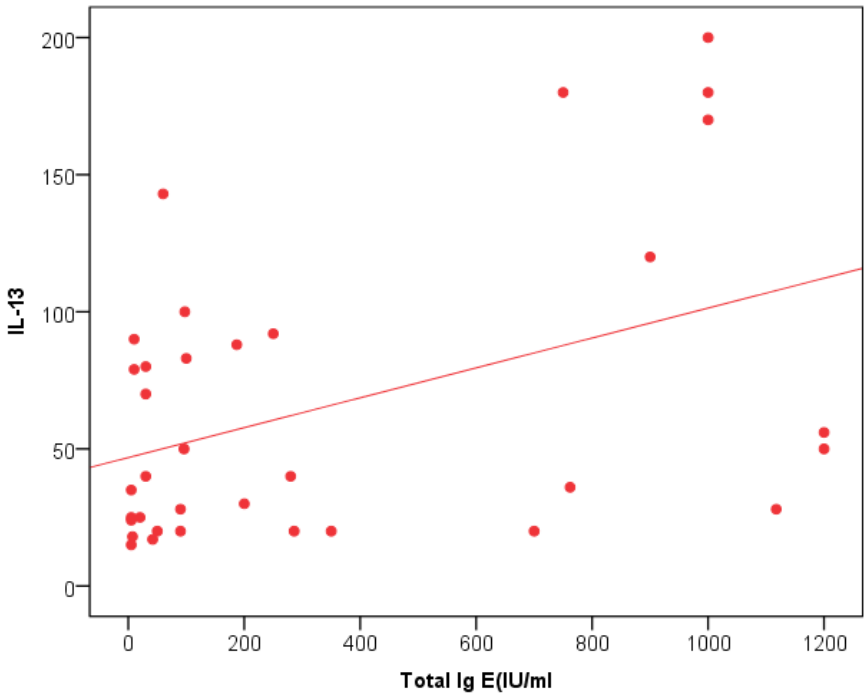


**Figure 1.** Correlation between serum IL-13 and total IgE levels in patients with bronchial asthma (r = 0.390, p = 0.020)

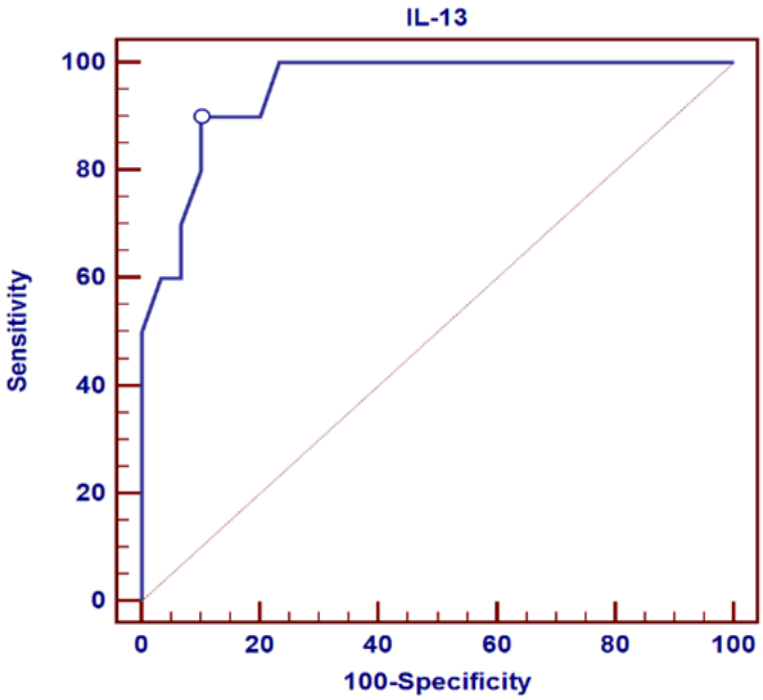


**Figure 2.** ROC curve illustrating performance of IL-13 (AUC=0.952) in discrimination between patients with severe asthma and those with mild to moderate asthma. (AUC: area under the curve)

## DISCUSSION

This study was carried out at Children's Hospital, Ain Shams University, in Cairo, Egypt, an Eastern Mediterranean country in the Northeast of Africa. Our findings pointed to the role of "A" allele in IL-13 rs20541 in increased susceptibility to bronchial asthma (as evident by the high significant difference between the "A" allele frequency in patients group as compared to controls). This supports the hypothesis that the replacement of the major "G" allele by the minor "A" allele corresponds to alteration in the structure of IL-13; specifically, in the α helix of the D domain. Accordingly, the neutrally charged glutamine is replaced by the positively charged arginine amino acid. This change in structure reflects a diminished affinity of IL-13 to its α2 receptor which is believed to function as a decoy receptor controlling inflammatory process.[12,13]

Similar findings were reported in previous studies performed by Resende et al.,[4] on adult Portuguese population and Halwani et al.,[14] on Saudi Arabian population. However, the later study reported a significant association between IL13 rs20541 SNP polymorphism and asthma severity. This association wasn't found in our results. This can be referred to the relatively small number of participants in each of the severity categories. Also, a recently published meta-analysis concluded that rs20541 polymorphism is a potential risk factor for asthma in people from different ethnicities.[15]

We couldn't find evidence for association between rs20541 SNP polymorphism and either IgE levels or allergic rhinitis. Similarly, Lu et al.,[3] did not find a significant association between IL13 SNPs and allergic rhinitis among Chinese children with asthma. Although, genetic predisposition is central in the development of asthma, and other chronic allergic diseases, yet the pathogenesis of these diseases is of multifactorial nature incorporating environmental and lifestyle factors.[16-18]

Interestingly, a prior meta-analysis reported a significant association between IL13 rs20541 SNP and allergic rhinitis among the Asian population but not Caucasians.[19] The lack of association to allergic rhinitis was also reported by Resende et al.[4] who attributed this to the direct functional effect exerted by IL-13 on the smooth muscle of the lower respiratory airways as compared to the influence of the vascular tone on the patency of upper respiratory airways.[20]

The proinflammatory role of IL-13 in airways of asthmatic patients has been extensively described in literature[21-24]. Hence, the statistically significant difference in levels of IL-13 in asthmatic patients versus healthy controls in this study was anticipated. IL-13 was also able to differentiate between patients in terms of asthma severity. Also the significant correlation between IL-13 and IgE levels found in this study came in accordance with those of previous studies [25-26] demonstrating the role of IL-13 as a primary regulator of IgE class switching, expression and secretion.

Despite our results contribute to a better understanding of the pathogenesis of bronchial asthma, the main limiting points are the relatively small sized sample, and that other environmental background factors and genetic variants that may contribute to the development of asthma in the studied population were not addressed.

Further studies are needed on larger scale populations for better identification of genetic variants of IL13.

## CONCLUSIONS

IL-13 rs20541 SNP polymorphism is associated with asthma in Egyptian children and serum IL-13 is linked to the severity of asthma.

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