

ORIGINAL ARTICLE

# Evaluation Gene Expression of Long Non-coding RNA and 5-Hydroxytryptamine $3A$ Receptor in Bronchial Asthma

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Received:Feb 13, 2024,  
Revised:Mar 01, 2024,  
Accepted:Mar 20, 2024,

DOI: 10.57238/jbb.2024.7304.1081



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article online

## Abstract

**Background** Bronchial asthma is a reversible chronic inflammatory condition of the airways. It is a complex clinical syndrome characterized by airway congestion, inflammation, and hypersensitivity to numerous stimuli. lncRNAs and the serotonin receptors, named 5-Hydroxytryptamine  $3A$  Receptor (5-HT $3A$ ), causes the release of a number of pro-inflammatory cytokines that are crucial in allergic asthma.

**Aim** Present study aimed to evaluate role of gene expression of lncRNA (and 5-HT $3A$  in asthma).

**Methods** In this study, 100 people with bronchial asthma (59 women and 41 men) between the ages of 2 and 61 were compared to 30 healthy people of the same age range (14 women and 16 men).

**Results** current results showed a significant correlation ( $p < 0.05$ ) between 5-HT $3A$ , lncRNA and bronchial asthma when a high gene expression (folding change) of these genes detected in asthmatic patients (2.62 and 2.49 respectively) compared to healthy control (1.00). The increased gene expression of these genes mainly appeared in females (2.05 and 2.03 respectively). Moreover, The highest mean folding of 5-HT $3A$ , lncRNA are looked in patients with familial asthma (2.80 and 2.99) compared to patients without family history (1.11 and 1.01 respectively).

**Conclusion** lncRNA and 5-HT $3A$  play significant role in development of bronchial asthma in present population.

**Keywords:** Asthma, 5-HT $3A$ , lncRNA, Gene expression.

## 1 Introduction

Bronchial asthma is a common chronic airway illness characterized by variable and recurring symptoms such as bronchial hyperresponsiveness and underlying inflammation. The clinical symptoms, severity, and therapeutic response of asthma are all determined by the interplay of these factors [1, 2]. In bronchial

asthma, airway constriction and the resulting obstruction with airflow is the major physiological event contributing to clinical symptoms. Acute exacerbations of asthma are characterized by a rapid contraction of bronchial smooth muscle (broncho-constriction) to restrict airways in response to numerous stimuli, such as allergens or irritants [3, 4]. The underlying process is yet unknown, however increased airway smooth

muscle mass has been associated to both mild and severe asthma [5]. Serotonin and long noncoding RNAs are known to play a crucial role in controlling healthy primary airway smooth muscle cells, however altered expression of these factors has been seen in CD8 T cells from asthmatic patients [6]. Only 1% of the human genome codes for proteins, whereas 75% is translated into RNA, according to genomic studies, indicating that the majority of the genome is used for control [7]. There is a novel class of non-protein coding RNAs called long non-coding RNAs. These RNAs are longer than 200 nucleotides and can control gene expression at the chromatin, transcription, and post-transcription levels. They are likely to be involved in innate immunity and viral replication [8,9]. LncRNAs have been shown to be differentially expressed during T cell maturation and differentiation. CD4+ T cell development and activation are aided by dendritic cells (DCs) and regulatory T cells (Tregs), which in turn are regulated by lncRNAs [9].

The monoamine neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) has many important physiological regulating functions. 5-HT has been shown to bind to seven different types of receptors, designated as 5-HT1-7. Each of these receptor groups is further subdivided [10,11]. The 5-HT3 receptor is the only member of the 5-HT receptor family that is not a G protein-coupled receptor; instead, it is a ligand-gated cation channel in the Cys-loop receptor superfamily with 9 exons. In response to serotonin, the 5-HT $_{3A}$  receptors on some PBMCs, such as monocytes and DC, initiate a cascade of signal transduction in the cells, resulting in the release of cytokines such as IL-6, IL-1, and IL-8/CXCL8 [11,12]. All of these cytokines have been shown to play an important role in the inflammatory response in asthmatic patients [13]. Present study focused on evaluation correlation between severity of asthma and gene expression of lncRNA (*ENST00000563434.1 (RP11-401.2)*) and 5-HT $_{3A}$  in different ages.

## 2 Materials and methods

### 2.1 Study groups

One hundred people participated in the current study (59 females, 41 males). The individuals were clinically

diagnosed by their doctors as having bronchial asthma. Patients were interviewed directly by using an anonymous questionnaire include; age, sex, the frequency of symptoms, drug, family history and smoking. Diagnosis of bronchial asthma case was carried out according to the treating physician and symptoms (i.e. wheeze, shortness of breath and cough) and supported by evaluation of IgE and spirometry assessment before and after treatment with improving of FEV1 more than 12%. The control group consisted of 30 seemingly healthy persons (16 male and 14 female) who were free of pathology at the time of the investigation; all of these individuals were age and gender matched to the patients. In this study, the control group was made up of people who had no history of systemic diseases. In addition, present study was in agreement with ethics of Al-Zahraa Teaching Hospital and verbal informed consent was obtained from all participants.

### 2.2 Classification of bronchial asthma

Depending on clinical criteria and reading of pulmonary functional test, the cases of bronchial asthma of patient above 5 year are classified according to severity to four degrees including: intermittent, mild persist, moderate persist and severe persist whereas other cases with age under 6 year are remain as unclassified.

### 2.3 Molecular study

All samples' total RNA was extracted using the AccuZol kit per the instructions provided by the manufacturer. Total RNA was reversely transcribed to complementary DNA (cDNA) using (cDNA kit, SINTHOL Company/Russia). Using quantitative real-time PCR (RT-qPCR), the expression levels of the PD1 and TIP2 genes were estimated. RT-PCR EvaGreen test was used to confirm the target. The manufacturer recommended a 25  $\mu$ l reaction volume, which is what was used throughout the process. The gene's expression. The mRNA levels of endogenous control gene  $\beta$ -Actin were amplified and used to normalize the mRNA levels of lncRNA (*ENST00000563434.1 (RP11-401.2)*) and 5-HT $_{3A}$  genes. Primers that used for RT-qPCR are listed in Table 1.

**Table 1:** Primer Sequences Used in RT-qPCR.

Gene	Primer	Sequence (5'→3' direction)	References
lncRNA (ENST00000563434.1 (RP11-4O1.2))	Forward	5'- AAGGAGACATTGACCAGATT -3'	[14]
	Reverse	5'- ATAACTCATGGCTAAGAGCT -3'	
5-HT <sub>3A</sub>	Forward	5'- GGTACCGGCAGTACTGGACT -3'	[15]
	Reverse	5'- CGGCGGATGACCACATAG -3'	
$\beta$ -actin (Reference gene)	Forward	5'-CTGGAACGGTGAAGGTGACA-3'	[16]
	Reverse	5'-CGGCCACATTGTGAACTTTG-3'	

**Table 2:** The case-control comparison.

Case-control Characters	Healthy controls	Cases (Asthma)	P value		
Age (years)					
Range	2-61	2-61			
Mean $\pm$ SD	29.1 $\pm$ 17.11	29.72 $\pm$ 16.27	0.977		
SE	3.177	1.635			
IgE(ng/ml)					
Range	24.329 – 419.398	2.447-38.293			
Mean	200.517	15.082	0.00001 *		
SD	73.166	9.627			
SE	7.3166	1.758			
Gender	N	%	N	%	
Female	14	47	59	59	0.307
Male	16	53	41	41	0.312
Total	30	100	100	100	

\*= Significant ( $p < 0.05$ ); SD= Standard Deviation; SE= Standard Error; N= Number

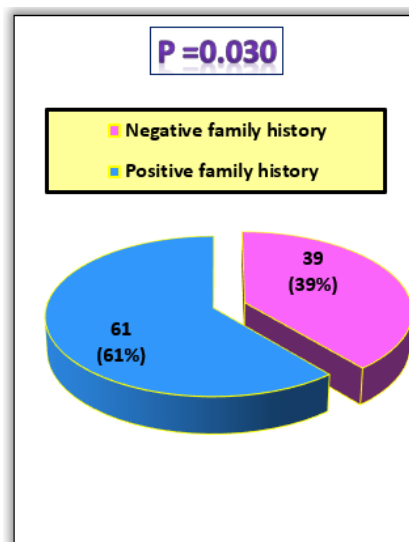
## 2.4 Statistical analysis

The information was converted into a computerized database structure. SPSS version 20 computer software (Statistical Package for Social Sciences) was used for statistical analyses, along with Microsoft Excel 2010 and social science statistics. The prevalence of variables such as gender, age, and asthma severity is calculated as a percentage. Since the data fit a normal distribution, we conducted an unpaired student's t test to see how much different bronchial asthma patients were from healthy controls. If the P value of an estimate was less than 0.05, it was considered statistically significant.

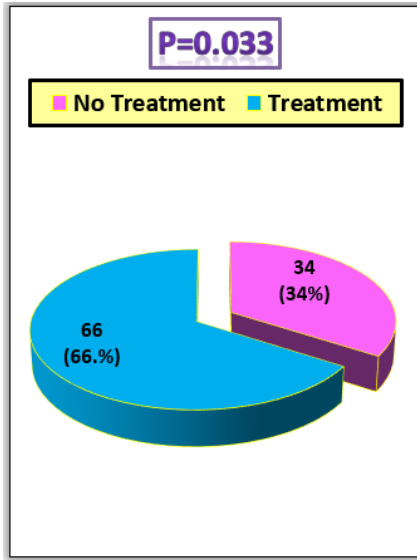
## 3 Results

Table 2 revealed there are no significant differences between patients and healthy individuals in the mean of age (29.1  $\pm$  17.11 and 29.72  $\pm$  16.27 respectively) ( $p=0.977$ ). The mean serum concentration of IgE significantly higher among cases with asthma (200.517ng/ml) compared to healthy controls (15.08ng/ml) ( $P<0.05$ ). Also this results showed that most asthmatic patients are females (59.00%) but this not reflect significant differences between patients and according to gender ( $p>0.05$ ). The current study, Fig-

ure 1, show a high proportion of asthmatic patients with a positive familial asthma (61.00%) with a significant probability ( $p=0.030$ ) in compared with patient without familial asthma (39.00%). Moreover, Figure 2 revealed that most patients in present study took treatment (66.00%).



**Figure 1:** Distribution of asthmatic patients according to family history.



**Figure 2:** Distribution of asthmatic patients according to treatment.

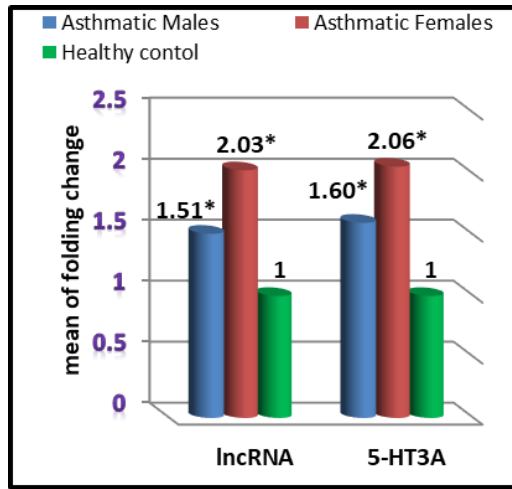
Analysis of relative gene expression was worked by using Real- Time Quantitative PCR and the  $2^{-\Delta\Delta ct}$  Method [17]. Table 3 showed a significant correlation ( $p < 0.05$ ) between asthma and gene expression of

*lncRNA* and 5-HT<sub>3A</sub> when the high gene expression (folding change) are appeared in asthmatic patients (2.49 and 2.62 respectively) compared to healthy control (1.00). the gene expression of *lncRNA* and 5-HT<sub>3A</sub> effected by gender as in Figure 3a, when increased gene expression of these genes are appeared in females (2.03 and 2.06 respectively) compared with males (1.51 and 1.60 respectively) and control group (1.00). Moreover, The highest mean folding of *lncRNA* and 5-HT<sub>3A</sub> are observed in patients with familial asthma (2.80 and 2.99) compared to patients without family history (1.11 and 1.01 respectively) and control group (1.00) as in Figure 3b.

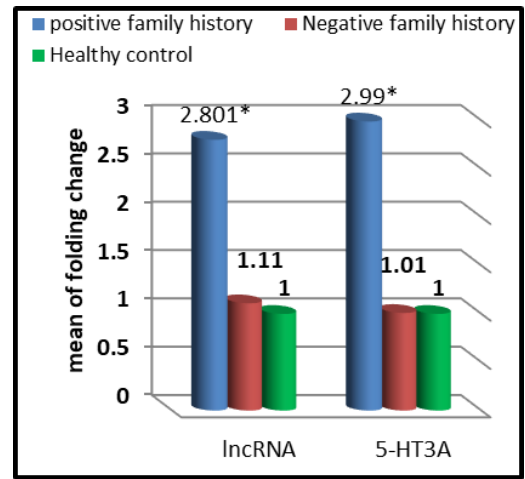
According to Table 4, The peak gene expression of *lncRNA* was raised mainly in sever persist asthma tailed by unclassified and moderate persist (5.15, 2.32 and 2.06 respectively). On other hand, the mean folding of 5-HT<sub>3A</sub> was raised in patients with the sever persist asthma, moderate persist asthma and mild persist asthma (2.69, 1.92 and 1.08 respectively). Although the gene expression of *lncRNA* and 5-HT<sub>3A</sub> have role in severity of asthma, their mean folding are not effected by medication in compared treated cases (2.89 and 1.38 respectively) with not treated cases of bronchial asthma (2.14 and 1.33 respectively).

**Table 3:** The case-control comparison.

Case-control	Mean CT(gene)	Mean CT(actin)	Mean $\Delta ct$ (test)	Mean $\Delta\Delta ct$	Mean Fold change ( $2^{-\Delta\Delta ct}$ )
<i>lncRNA</i>					
Patients	16.93	15.89	1.04	-1.32	2.49*
Control	18.14	15.78	2.36	0.00	1.00
5-HT <sub>3A</sub>					
Patients	16.10	11.77	4.33	-1.39	2.62*
Control	17.61	11.89	5.72	0.00	1.00



(a)



(b)

**Figure 3:** Distribution of mRNA, gene expression of *lncRNA* and 5-HT<sub>3A</sub> according to gender (a) and (b). \* = significant association in compared with control groups( $p < 0.05$ ).

**Table 4:** The mRNA expression of 5-HT<sub>3A</sub>, *lncRNA* and PD-1 according to severity \ treatment of asthmatic patients and control group.

Case-control	Mean CT(gene)	Mean CT(actin)	Mean $\Delta ct$ (test)	Mean $\Delta ct$ (control)	Mean $\Delta \Delta ct$	Mean Folding
<i>lncRNA</i>						
Unclassified	17.032	15.89	1.142	2.36	-1.218	2.32*
Intermittent	17.949	15.89	2.059	2.36	-0.271	1.20*
Mild Persist	17.493	15.89	1.603	2.36	-0.301	1.23*
Moderate Persist	17.202	15.89	1.312	2.36	-1.048	2.06*
Sever Persist	15.855	15.89	-0.035	2.36	-2.365	5.15*
Control	18.14	15.78	2.36	2.36	0.00	1.00
5-HT <sub>3A</sub>						
Unclassified	17.536	11.77	5.766	5.72	0.046	0.96
Intermittent	17.538	11.77	5.768	5.72	0.048	0.96
Mild Persist	17.377	11.77	5.607	5.72	-0.113	1.08
Moderate Persist	16.547	11.77	4.777	5.72	-0.943	1.92*
Sever Persist	16.06	11.77	4.29	5.72	-1.43	2.69*
Control	17.61	11.89	5.72	5.72	0.00	1.00
<i>lncRNA</i>						
Treatment	16.714	15.89	0.824	2.36	-1.536	2.89*
Nontreatment	17.147	15.89	1.257	2.36	-1.103	2.14
5-HT <sub>3A</sub>						
Treatment	17.024	11.77	5.254	5.72	-0.466	1.38
Nontreatment	17.077	11.77	5.307	5.72	-0.413	1.33

\*= significant difference between severity/treatment and gene expression ( $p < 0.05$ ).

## 4 Discussion

Table (2) shows the mean age of patients are  $29.72 \pm 16.27$  and  $29.1 \pm 17.11$  for control group ( $P = 0.977$ ), this consistence with Mishra et al.,(2004) who found the mean of age of asthmatic patients  $30 \pm 11.2$  and controls  $29.23 \pm 12.94$  ( $P > 0.05$ ) but current results disagree with Vergara et al., (2010), who studied 429 non-related adult asthmatics and 401 control group and reported that mean age was  $36.15 \pm 18.32$  and  $34.98 \pm 17.8$  years, respectively [18,19]. Nagasaki et al., (2013) and Gibson et al., (2010) assumed the prevalence of bronchial asthma in adults and older asthmatic patients may be due to inadequate treatment or healthcare of asthma, increase smoking or exposure to air pollutions and increase other pulmonary diseases or microbial infections in airways in some population (especially urban regions) [20,21].

In present work recorded most asthmatic patients are females (59.00%) with age range from 16 to 45 year . Asthma is more common in boys than in girls among children, it has also been observed . However, as adults, women have a higher prevalence of asthma than men , this agree with results of Chen et al., (2003) that found Female-to-male asthma hospitalization incidence peaked at 2.8 for those aged 25-3 ,then declined with advancing age [22], this may be due to high life activities such as work and exercise, which increase sensitivity to allergens, as well as hormonal changes in females (as during pregnancy and menstrual) may increase the frequency of asthma khaz et al., 2014 [23]. Asthma risk is significantly influenced by the sex effect,

which varies significantly over the lifespan. Insight into the causal pathways connecting age, gender, and asthma is lacking. Gender and age-related differences in airway size relative to lung size may account for these disparities [24]. Adult females were more affected by asthma, according to Chhabra (2005), because of the increased likelihood of sex-related hormonal or metabolic variations, which may have a role in the pathogenesis of asthma. Because of their more sensitive airways, adult women have a greater incidence of asthma than do males, according to certain research. This is probably connected to the fact that female sex hormones increase cytokine release and total IgE levels [25]. However, estrogen stimulates FoxP3+ regulatory T (Treg) cells while progesterone prevents histamine release from mast cells [26]. This study also shows a significant correlation between serum level of IgE and bronchial asthma ( $P < 0.001$ ). Bronchial asthma is characterized by an increase in serum IgE owing to the protein's central involvement in the development of bronchial hyperresponsiveness and the production of mediators from mast cells that intensify the inflammatory response [27,28].

Present study confirmed results of other studies that showed evaluated gene expression of *LncRNA* with increasing severity onset of asthma [29]. Also current finding in line with study of Persson et al., (2015) that supported the role of *lncRNA* in therapy-resistant asthma [30]. Different profiles of *lncRNAs* in immunological processes have been observed. Different *lncRNAs* are differentially expressed in CD8

T cells, according to a genome-wide RNA sequencing investigation. During T helper cell development, *lncRNAs* may function as enhancer elements. The *lncRNA* is induced in IL-13 in primary esophageal epithelial cells and is raised in eosinophilic esophagitis, another allergic inflammatory condition [31]. Current study showed significant correlation ( $p < 0.05$ ) between 5-HT $_{3A}$  and asthma. When allergens or other stimuli enter the airways of asthmatic patients, they cause increased gene expression of 5-HT $_{3A}$ , which leads to the production of IgE antibodies by B cells. These antibodies activate the classical complement system pathway, which results in the production of platelet activating factors [32]. These stimuli cause platelet serotonin resealing at inflamed areas. Some PBMC cells respond to serotonin by increasing Ca $^{2+}$  influx; these cells, which include monocytes, macrophages, T cells, and B cells, are subsequently drawn to sites of inflammation. Pro-inflammatory mediators like IL-6, IL-1B, and IL-8/CXCL8 are ultimately caused by this bivalent cation ion [33]. This research agrees with an Iranian study that indicated that people with asthma had considerably higher levels of 5-hydroxytryptamine  $3A$  subtype receptor gene expression in their peripheral blood mononuclear cells than those without asthma [15]. The current findings are consistent with those of Ahangari et al. (2015), who found that asthma patients' peripheral blood mononuclear cell gene expression was considerably higher than that of the normal group ( $P = 0.003$ ) [34]. Taking into account the findings of this study, Ahangari et al. conclude that 5-HT $_{3A}$  receptors can be employed as a diagnostic biomarker for asthma; however, more research is needed on a bigger population. Also, the possible role of this receptor in bronchoconstriction could lead to the creation of antagonists as a new treatment for asthma [13].

In present study, gene expression of 5-HT $_{3A}$ , *lncRNA*, are not effected by treatment this may be due to that patient not complete the course of treatment or may be that traditional drags (as corticosteroids) not effected on these genes and require to novel drugs inhibited their expression during onset of asthma. Moreover, we did not get on a studies about this subjects but there are few modern study in additional to present study suggest that 5-HT $_{3A}$  and *lncRNA* a good target for novel therapeutic approaches to reduce severity of asthma and recommended to other lateral study to confused on this very important point [34–36]

## 5 Conclusion

5-HT $_{3A}$  and *lncRNA* have a significant role in development of bronchial asthma and the highest expression of these genes mainly observed in females and in patients with familial asthma. Moreover, increase gene

expression of 5-HT $_{3A}$  and *lncRNA* are associated with increase severity of asthma.

**Conflict of Interest:** No conflicts of interest exist between the authors and the publication of this work.

**Ethical consideration:** The ethical committee approved the study at Wasit University, Wasit, Iraq.

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#### How to cite this article

Mubark N.N.; Shahadha M.A.A.; Abbas I.M.; Evaluation Gene Expression of Long Non-coding RNA and 5-Hydroxytryptamine  $3A$  Receptor in Bronchial Asthma. *Journal of Biomedicine and Biochemistry*. 2024;3(1):26-33. doi: 10.57238/jbb.2024.7304.1081