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Association between rs3806798 Polymorphism of IL-15 Gene and its Serum Level in Atopic Dermatitis Patients

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Abstract: Atopic dermatitis (AD) is result in several consequences, included disruption of barrier, pruritus and inflammation including releasing type-2 cytokines. High levels of IL-15+dendritic cells and T cells were produced in both dermis and epidermis of lesional skin, that suggests a probable interaction by IL-15. In current study, the serum levels of IL-15 were suggested to correlated with single nucleotide polymorphisms (SNPs) of its gene in the rs3806798. After obtaining approval by the Ethics Committee, this study carried at the Specialist Centre for Allergy (Al-Russafa, Baghdad, Iraq) on patients with symptoms indicative of atopic dermatitis, with the goal to evaluate the changes in some biomarkers of allergic atopic patients. The study included 85 patients who were diagnosed with atopic dermatitis, and 40 healthy control. from November 2021 to March 2022. Six milliliters of venous blood were withdrawn from each subject by vein-puncture under aseptic technique by syringe one part in a sterile EDTA tube for testing the eosinophils count, second part were dispensed in a sterile EDTA tube for DNA extraction, and the third part dispensed in a sterile gel tube to centrifuge at 3000 r.p.m for fifteen minutes at room temperature to separate the serum and dispensed into three sterile Eppendorf tubes which tightly closed and kept at -20°C till assayed.,as our knowlege this is the first study investigating *IL-15* gene SNPs that correlated with serum levels in cases with Atopic dermatitis therefor interleukin15 was chosen. The finding of the current study indicates that variants of *IL-15* gene rs3806798 are more common in cases with AD than HC. In another hand, the effect of these SNP on development of AD is depend on status of mutant TT.

Keywords: polymorphism, IL-15, Atopic dermatitis.

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Introduction

Atopic dermatitis is a relapse and chronic dermatitis that occur through the childhood or infancy. About (5-20) % of worldwide population in the childhood stage. This disease is significantly widespread in urban locations and developed countries. Several factors can effect on the eczema development, including family history (particularly, maternal history) is a strong predictive risk factor. However, there are several environmental factors, such as more exposing to airborne contamination and non-enough exposing to microorganisms in earlier stage of childhood (1,2). This disease is a hereditary condition that common in families. However, there is no apparent line of heredity, which describes why some healthy parents could have affected children, barring simple dominant heredity. On another hand, some affected parents have unaffected

children, excepting a simple recessive trait (3). In childhood stage, males are more likely to suffering from AD. However, females are more likely to get the condition(4).

Atopic dermatitis is significantly showing emotional symptoms in addition to physical symptoms. Patient with AD have been liven significantly with self-esteem and life quality, as well as anxiety, depression and raised disturbances of sleep(5,6). The fact that stress aggravated AD symptoms can lead to a downward spiral with stress from the AD worsening the flare, which can aggravate stress (6).

In addition to defects of epidermal barrier,the immunological factors of AD pathogenicity were taken in consideration. Many disorders lead to production of Th2 cells, which resulting in cytokines release, such as IL-13, IL-5 and IL-4, as well as raise the IgE formation, in order to raise the inflammatory reaction in the skin, and aggravate the defect of its barrier. Additionally, the effect of skin inflammation in AD-suffering individuals from exerts well-known Th2 cells and to releasing Th17 and Th22 cells and cytokines, include IL-22, IL-19 and IL-17. The T cell response and the cytokines domination released by them varied considerably in the AD-aggravating and -remising stages (7).

Specially, in AD, high levels of IL-15+dendritic cells and T cells were produced in both dermis and epidermis of lesional skin, that suggests a probable interaction by IL-15. Additionally, activation of T-cell may be mediated by IL-15 on the surfaces of dermal fibroblasts after extended stimulating TNF-α(8). These results are agreed with previous researches which report that the epidermal keratinocytes cannot express the IL-15 in normal conditions, but when the body subject the inflammation, both of neutrophil and eosinophil induced in order to produce IL-15 (9,10).

The aim of this study detects a serum level concentration of Interleukin 15 and gene polymorphism rs3806798 in atopic dermatitis Iraqi patients.

Materials and methods

The current cross-sectional, retrospective study incorporated eighty-five AD-suffering cases and forty healthy controls. It composed individuals with AD from the Department of Specialist Centre for Allergy (Al-Russafa, Baghdad, Iraq). The AD diagnosis in each case was recorded after obtaining the medical history and using dermatological examination. Six milliliters of venous blood were withdrawn from each subject by vein-puncture under aseptic technique by syringe. The blood samples were divided into three parts; one part two milliliters of the blood from peripheral venous were dispensed in a sterile EDTA tube for testing the eosinophils count, second part two milliliters of the blood from peripheral venous were dispensed in a sterile EDTA tube for DNA extraction, and the third part two milliliters of the blood sample dispensed in a sterile gel tube and left for about two hours to clot and then centrifuged at 3000 r.p.m for fifteen minutes at room temperature to separate the serum and dispensed into three sterile Eppendorf tubes which tightly closed and kept at -20°C till assayed. Serum total-IgE estimation was calculated automatically and printed by ELISA printer. IL-15 serum level was calculated utilizing a kit of enzyme-linked immunosorbent assay (ELISA) (BioSource USA), as well as the manufacturer instructions were performed. The kit detection ranges were 3.12–200pg/mL. Samples of DNA were extracted using kit of Mini DNA

extraction based on the instructions of manufacturer (EasyPure Genomic DNA KIT Trans Gene.biotech.EE101-01).

The SNPs in the rs3806798 loci of the *IL-15* gene were estimated by the amplification using quantitative PCR (qPCR) in high resolution melting assay. The sequence of forward primer is CCGGGTGTCTTCTTCCAACA and reverse primer is CTCTTGGTCCCCGCACAG.

Statistical analysis

The SPSS analysis was carried out in order to evaluating the significant variations in the obtained allele among the patients and healthy controls. To calculating the 95% confidence intervals (CIs) and the odds ratios (ORs), a logistic regression model was utilized.

Results and discussion

The current study, The IL-15 levels were significantly increased in serum of AD cases in comparison with HC, mean±SD (22.283±7.713 *vs.* 13.268±3.334) *p*-value < 0.001. The Concentration of Interleukin-15 in Atopic dermatitis patients-controls in ELISA was measured as shown in Table (1):

Table (1): The Concentration of interleukin-15 in atopic dermatitis patients-controls

ELISA		Atopic dermatitis		Controls		P value
		No	%	No	%	
IL 15 (ng/dL)	<10ng/dL	1	1.2	3	7.5	0.0001*
	10---	3	3.5	25	62.5	
	15---	30	35.3	9	22.5	
	20---	34	40.0	3	7.5	
	25---	12	14.1	-	-	
	=>30ng/dL	5	5.9	-	-	
	Mean±SD (Range)	22.283±7.713 (8.570-58.273)		13.268±3.334 (9.651-22.822)		0.0001#
	*Significant variation among percentages utilizing Pearson Chi-square test (χ^2-test) at 0.05 level. # Significant variation among 2 independent means utilizing students-t-test at 0.05 level.					

Table 2 shows the percentage of IgE immunoglobulin of atopic dermatitis patients and healthy controls, so the results were highly significant P value = 0.0001. The table also studied the eosinophil measurement, and the results observed that there were no significant variations with eosinophil cells (*p*-value = 0.553).

Table (2): Total IgE and eosinophil in atopic dermatitis patients -controls

		Atopic dermatitis		Controls		P value
		No	%	No	%	
Total IgE (IU/mL)	<50IU/mL	39	45.9	40	100	0.0001*
	50---	4	4.7	-	-	
	100---	5	5.9	-	-	
	150---	3	3.5	-	-	
	200---	10	11.8	-	-	
	250---	8	9.4	-	-	
	=>300IU/mL	16	18.8	-	-	
	High (=>180)	35	41.2	-	-	0.0001*

		Atopic dermatitis		Controls		P value
		No	%	No	%	
	Normal (<180)	50	58.8	40	100	
	Mean±SD (Range)	157.367±158.276 (10.324-487.879)		14.622±1.853 (12.292-19.727)		0.0001#
Eosinophil	High (>4)	17	20.0	7	17.5	0.741
	Normal (1-4)	68	80.0	33	82.5	
Eosinophil	<1.0e	16	18.8	6	15.0	0.695
	1.0---	16	18.8	11	27.5	
	2.0---	22	25.9	10	25.0	
	3.0---	14	16.5	6	15.0	
	4.0---	10	11.8	2	5.0	
	=>5.0e	7	8.2	5	12.5	
	Mean±SD (Range)	2.7±2.0 (0.21-10.15)		2.5±1.5 (0.50-6.26)		0.553
*Significant variation among percentages utilizing Pearson Chi-square test (χ^2-test) at 0.05 level.						
#Significant variation among 2 independent means utilizing students-t-test at 0.05 level.						

Interleukin 15 was studied with age and gender of patients and healthy subjects, and the result showed is highly significant level (the *p*-value = 0.01), with age, gender, BMI, IgE, eosinophilia and duration of disease respectively. These results are shown in the table (3).

Table (3): Correlation IL15 with age, gender, BMI, IgE and eosinophilia atopic dermatitis patients

	Total IgE (IU/mL)	Eosinophil	IL 15 (ng/dL)
Atopic dermatitis (n=85)			
Age (years)	-0.397**	-0.027	-0.019
	<0.001	0.805	0.864
BMI (Kg/m2)	-0.045	-0.066	-0.004
	0.682	0.547	0.974
Duration of disease (years)	-0.039	0.067	-0.059
	0.723	0.543	0.589
Total IgE (IU/mL)	-	0.170	0.166
	-	0.119	0.128
Eosinophil	0.170	-	-0.007
	0.119	-	0.946
IL 15 (ng/dL)	0.166	-0.007	-
	0.128	0.946	-
Controls (n=40)			
Age (years)	0.272	0.036	0.144
	0.090	0.823	0.374
BMI (Kg/m2)	0.177	0.338*	-0.182
	0.275	0.033	0.260
Duration of disease (years)	-	-	-
	-	-	-
Total IgE (IU/mL)	-	0.081	0.425**
	-	0.621	0.006
Eosinophil	0.081	-	-0.332*
	0.621	-	0.037
IL 15 (ng/dL)	0.425**	-0.332*	-
	0.006	0.037	-
*Correlation is significant at the 0.05 level. ** Correlation is highly significant at the 0.01 level.			

Table (4): Interleukin 15 gene polymorphisms (rs3806798)

Genotyping		Atopic dermatitis		Controls		OR	95%CI	P value
		No	%	No	%			
HRM IL15	Wild TT	21	24.7	31	77.5	Ref	-	0.001*
	Mutant AA	45	52.9	1	2.5	66.43	8.49-519.9	0.0001*
	Hetero TA	19	22.4	8	20.0	3.506	1.297-9.48	0.012*

Figure (1) showed the genotype of the wild type, the mutant, and the hetero in HRM qPCR, in patients and healthy control, the results were Wild type TT, the mutant AA and hetero TA. The study showed a percentage of the mutated type in the patient 52.9, while in the healthy 2.5.

Figure (1) show the Genotypes Wild and mutant then hetero types atopic dermatitis patients and controls.

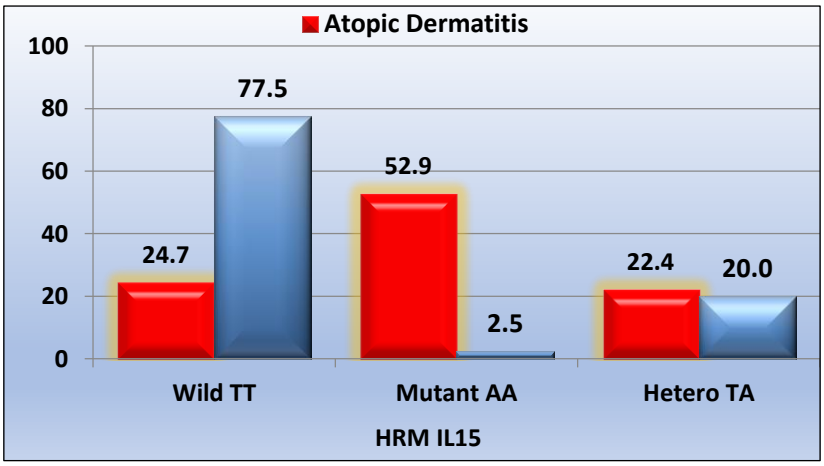

Figure (1): Genotyping Wild TT, Mutant AA and Hetero TA.

The table 5 was show correlation between IL15 serum level and gene polymorphisms. Results observed no significant difference between serum level and gene polymorphisms.

Table (5): Correlation between IL15 serum level and gene polymorphisms

#		IL 15 (ng/dL)			
		Atopic dermatitis		Controls	
		No	Mean±SD	No	Mean±SD
Total IgE (IU/mL)	High (=>180)	35	23.689±4.848	-	-
	Normal (<180)	50	21.299±9.126	40	13.268±3.334
	P value		0.161		
Eosinophil	High (>4)	17	21.729±4.788	7	12.135±2.906
	Normal (1-4)	68	22.422±8.308	33	13.509±3.409
	P value		0.743		0.329
HRM IL15	Wild TT	21	22.172±9.864	31	13.122±3.333
	Mutant AA	45	22.754±7.441	1	12.175±
	Hetero TA	19	21.291±5.709	8	13.973±3.671
	P value		0.788		0.778
#Significant variation among 2 independent means utilizing Students-t-test at 0.05 level.					
^Significant variation among more than 2 independent means utilizing ANOVA-test at 0.05 level.					

Discussion

Atopic dermatitis is an autoimmune disease which include inflammatory reaction effected via several genetic and environmental factors. Decreasing in expression of IFN- via the systemic immune response is considered as an essential property of AD in acute lesions of skin. The declining in expression of IFN- may resulting in the raised profile of Th2 cytokine and formation of IgE because of IFN- can inhibit the Th2 cells proliferation and IgE creating.

IL-15 is a cytokine which have function in both of innate and adaptive immune response and it is broadly expressed by variable cells. Furthermore, it works as a growth factor and allows the NK, B and T cells surviving by suppressing apoptosis during the down-regulation of pro-apoptotic and up-regulation of anti-apoptotic factors (11). IL-15 has been involved in the pathogenesis of different auto-immune and inflammatory disorders, including dermatomyositis**,** polymyositis, Systemic lupus erythematous (SLE) and rheumatoid arthritis (12). It was investigated that IL-15 have role in dermatologic disorders whereas its expression in pustular palmoplantar psoriasis and psoriatic plaques is high. However, It is lower expressed in acute atopic dermatitis (13).

In the current finding, there was highly significant serum level of IL-15 in individuals with AD in comparison with HCs. This result was disagreed Barahmani *et al.*, (2010) who reported that no significantly variations among the serum levels of cases and HCs. It is may be due to 54% of their individuals were atopic. In AD, IgE and Th2 cytokines (such as IL-13 and IL-4) are increased. Hence, acute skin lesions, the peripheral blood Interferon-γ (IFN-γ) and Th1 cytokine are reduced. The increased IgE and the inflammation may be because of reducing in IL-15(14)

IL-15 has variable functions in developing, maintaining, and profiling the memory CD8+ T cells, NK cells which are considered as a major producer of INF–γ that is main contributor in the development of AD (15). Its role has basically associated with cancer and autoimmune disorders. In previous studies, it was reported that the expression of IL-15 mRNA was specific for T cells, dermal fibroblasts, macrophages and keratinocytes in inflammation of skin, with higher expression in psoriasis in comparison with AD (16). Our finding about the IL-15 epidermal expression in AD cases is in agreed with previous studies which reported that the epidermal keratinocytes cannot expressed IL-15 in the normal conditions, but the production of IL-15 by neutrophil and eosinophil is induced under inflammatory conditions (16,17). When the regulatory T cells is cultured in contact with IL-15 and dermal fibroblasts, these T cells were highly proliferated in an antigen-independent manner, these conditions analogous to those appeared in chronic inflammation skin (18). In this context, Sakashita *et al.*, (2008) show high increasing in expression of IL-15 by fibroblasts in lesional AD, resulting in block T-cell lead to cause chronic inflammation in AD.

Moreover, the finding of the present study show highly significant of IgE (p-value 0.0001). The explanation of these results is the induction of IgE formation as well as the Th2 cytokines may be critical in beginning the acute inflammatory reaction of AD by

inflammatory cells recruitment into the acute lesions of skin. IgE has role in pathogenesis of AD through facilitation of allergen by Langerhans cells and presenting it into skin T cells. The reduced release of IL-15 by peripheral blood mononuclear cell (PBMC) in cases with AD observed in the study gives evidence that the IL-15 dysregulation may haves role in the AD pathogenesis. This reduce in IL-15 release was also proved by a reduce in the expression of membrane-bound IL-15 by the monocytes of individuals with AD and a reduced IL-15 mRNA expression in the acute and chronic skin lesions of AD in comparison with that in skin lesions of psoriasis (19). The current study observed there is no significant variation in eosinophils level in AD, whereas this result agreed with Jenerowicz *et al.*, 2007 that reported the patients with mild to moderate AD has less eosinophils levels than severe AD, without the significantly variation (20). Immunoglobulin E (IgE) has a unique position among immunoglobulins. Its serum concentration may elevate many folds response to specific inducers, where its levels are elevated in allergic diseases like urticarial, atopic dermatitis, allergic bronchial asthma and allergic rhinitis. There no significantly variation in eosinophilia among patients and HCs. In a previous study, the eosinophils existence in the blood of patients with atopic dermatitis, eosinophils are however part of the mixed perivascular inflammatory infiltrate within the dermis of AD patients. Additionally, the blood eosinophilia is existed in the higher percentage of AD patients correlating nearly with the severity. In blood, the eosinophilia was reported to be more pronounced if the AD was related to respiratory allergic diseases (21).

In this study showed investigated the contribution of IL-15 genetic polymorphisms to the development of AD. Interleukin 15 gene polymorphisms rs3806798 in AD Genotyping Wild TT, Mutant AA and Hetero TA the P value 0.001,0.0001and 0.012 respectively were high significant. The correlation between IL15 levels with genetic polymorphisms in AD Wild TT Mean±SD 22.172±9.864, Mutant AA 22.754±7.441 and Hetero TA 21.291±5.709 but no significant difference p value 0.788. more of study proven IL15 play important role in many autoimmune diseases, such as IL-15 gene polymorphism rs2857972 GG and rs1057972 TT variants are more prominent in celiac families than controls (22). Studied reported the IL-15 rs2254514 polymorphism as a possible susceptibility marker in ulcerative colitis and rs2857261, rs10519613, rs1057972, and g96516 SNP polymorphisms demonstrated a possible association between g.96516 A/T and increased psoriasis risk, In another studied IL-15 gene polymorphisms, IL-15 serum levels, and their effects on rheumatoid arthritis activity. They showed that 14035 A/T and −260 A/G polymorphisms increased IL-15 serum levels and serum RF isotypes and influenced rheumatoid activity (23). Associations between IL-15 and clinical symptoms have been studied in other autoimmune diseases and many studied definite that is IL-15 gene polymorphisms in conjunction with human leukocyte antigen HLA (24). Other studied found an SNP in the distal promoter region of ST2 (−26999G/A) that showed a significant association with AD during our series of genetic association studies within the *IL1R* gene cluster(25,26).

Conclusion

The finding of the current study indicates that variants of *IL-15* gene rs3806798 are more common in cases with AD than HC. In another hand, the effect of these SNP on development of AD is depend on status of mutant TT. In fact,as our knowlege this is the first study investigating *IL-15* gene SNPs that correlated with serum levels in cases with AD although the limitations previously mentioned.

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