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Research Article

CHEMISTRY

Role of serum expression of long non-coding RNA growth arrest-specific 5 (GAS5) in Egyptian patients of Behçet's disease

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KEY WORDS

Behçet's disease, Gas5, HB, PLT, WBC

ABSTRACT

Behçet's disease (BD) is a chronic inflammatory condition that recurs and is characterized by oral and vaginal ulcerations, ocular symptoms, and other systemic involvement. The study's objective was to evaluate the degree of growth arrest-specific 5 (GAS5) expressions in BD as an autoimmune disease. Thirty-five patients with BD (24 males and 11 females), and 30 healthy controls (22 males and 8 females) were included in this study. Sera were separated from blood samples and stored at -80°C until the time of analysis. These sera were used in Long noncoding extraction and detection of fold change of the gene GAS5 using real time PCR. When cases were compared to controls, there was a statistically significant rise in GAS5 expression (P 0.0001). With an AUC of 0.743 (95% confidence interval (CI): 0.598-0.888; sensitivity = 74.3, specificity = 100%), the ROC curve demonstrated that Lnc RNAs are useful in discriminating BD from healthy controls). This study proved that Lnc RNA GAS5 could be considered as a new diagnostic biomarker for Behçet's disease.

Introduction

Behçet's disease (BD) is a chronic relapsing inflammatory multisystem disease of unknown cause characterized by recurrent oral aphthous ulcers, vaginal ulcerations, ocular symptoms (e.g., uveitis, conjunctivitis), and further systemic involvement depending on the severity of the disease. An alternative term for Behçet's illness is malignant aphthosis **(Bettiol *et al*., 2020).**

An autoimmune process, an infectious or environmental factor, and, or a genetically susceptible individual all has been found to produce Behçet's illness. The interplay of a certain genetic background with environmental or viral variables could have a role in the immunological dysregulation that ripens this disease to some extent. By increasing the likelihood of clinical symptoms, the polymorphism of the vitamin D receptor (VDR) may also play a part in the etiology of disease **(Dal *et al.,* 2019)**. Now, autoimmunity can no longer fully explain the condition, it is thought to be somewhere in the middle of auto-inflammatory and autoimmune. Behçet's illness is now understood to be an auto-inflammatory disease that is induced by external stimuli in genetically vulnerable people **(Kulaber *et al.,* 2007)**.

Long non-coding RNAs (LncRNAs) are RNA molecules that have a length greater than 200 nucleotides **(Tano *et al.,* 2012).** RNAs known as LncRNAs can only code for a small number of proteins. At several stages of gene expression, including transcription, post-transcriptional, translation, post-translation, and epigenetic modification, LncRNAs interact with RNA, DNA, and proteins **(Hassan *et al*., 2015).**

A transcript called GAS5 (human growth arrest-specific transcript 5) contributes to growth arrest in people. With 12 exons and 11 introns that encode the same 10 snoRNAs in corresponding introns with a short open reading frame (ORF), one LncRNAs, a multi-snoRNA host gene on chromosome 1q25.1, is spliced to create two mature LncRNAs **(Xue *et al*.,2017).**

The goal of this study was to assess the levels of expression of growth arrest-specific 5 (GAS5 (NR 002578.2) by PCR method in Behçet's illness to see whether GAS5 may be used as a new biomarker for diagnosis, and to correlate its level with disease characteristics.

Material and Methods

A total of 65 participants were included in this study which were two groups:

Group I: 35 Behçet's patients [11 females (31.4%) and 24 males (68.6%)] underwent evaluation and assessment at the Fayoum University Hospital's, Rheumatology department either as inpatients to undergo departmental investigations or as outpatients. They were identified as Behçet's patients based on the International Study Group criteria for Behçet's disease **(Davatchi *et al*., 2014).**

Individuals under the age of 18 and those who had diabetes, kidney failure, liver failure, heart failure, or cancer were also disqualified from the trial.

Group II: A control group of 30 healthy people [8 females (26.7%) and 22 males (73.3 %)] were also included in the study.

The Ethical Committee of Fayoum University's Faculty of Medicine gave its approval to this study (numbered R 320), which was conducted in accordance with the Helsinki Declaration (2009). After being told of the study's purpose, the participants' legal guardians verbally agreed in each case.

Detailed history taking and full clinical examination was performed. Behçet's Disease Current Activity Form (BDCAF) score was calculated **(Bhakta ET AL., 1999)**.In addition to complete laboratory investigations; the detection of GAS5 expression level (NR_002578.2) in serum was done.

Blood sample collection and storage:

10 mL of blood sample was taken from each person and collected in a tube without anticoagulant, left at 37°C for half an hour, and then centrifuged for 10 minutes at 3000 rpm. Sera were separated and stored at -80°C until the time of analysis. These sera were employed in long noncoding extraction and real-time PCR measurement of GAS5 (NR 002578.2).

Long non coding RNAs extraction:

Using an iRNeasy mini kit and a technique for purifying blood total RNA, including long noncoding RNA (Qiagen, Valencia, CA, USA), GAS5 (NR 002578.2) gene expression levels in the serum could discovered

The NanoDrop® (ND)-1000 spectrophotometer has been used to measure and quantify the purity of RNA samples (Nano-Drop Technologies, Inc. Wilmington, USA).

Conversion of RNA into complementary DNA (cDNA) by Revers transcription (RT)

The miScript II RT kit (Qiagen, Valencia, CA, USA) was used to perform reverse transcription on total RNA in a final volume of 20 uL RT reactions.

Quantitative Real-time PCR (qPCR) for detection of long-non coding RNAs

The RT2 SYBR Green ROX q PCR Master Mix kit and method for quantifying long non-coding RNA were used to perform this stage (Qiagen, Valencia, CA, and USA).

The programing of real-time cycler was performed according to the table below (DNA-technology thermo cycler, DT light 4S1, Russian).

Table (1): Real-time cycler programming

Cycles	Duration	Temperature (ºC)
1	10 min.	95
40	15 s	95
40	min	60

The serum expression levels of the investigated LncRNAs GAS5 were evaluated using pre-made primers for GAS5 and GAPDH, with GAPDH serving as an internal control. The cycle threshold in real-time PCR is the requisite number of cycles for the fluorescent signal to pass through the threshold (Ct). It was assessed by comparing gene expression to an internal control (2Ct). For the relative fold change, 2Ct was used.

Melting curve tests were performed following the completion of the PCR cycles to ensure the precise generation of the anticipated PCR result. Standardization the expression pattern and quantification of the target long non-coding RNA in comparison to other genes could be determined by GAPDH.

The cycle threshold (Ct) value could be defined as the number of qPCR cycles required for the fluorescent signal to cross a predefined threshold. By deducting the GAPDH Ct values from the target Ct values, Ct was calculated.

Using the following formula the expression level of the long noncoding RNA Gas5's fold change was calculated. At subtracting the ΔCt of the control samples from the ΔCt of the disease samples we can obtain ΔΔCt.

When the FC is positively charged, the long non-coding RNA is up-regulated; when the FC is negatively charged, it is down-regulated. Because −ΔΔCt for control participants equals zero and 20 equal's one, the control value was taken to equal 1.

Statistical analysis of data*:*

SPSS software statistics computer package version 18 was used to arrange, tabulate, and statistically analyze the data collected (SPSS Inc, USA). The mean, median, standard deviation (SD), standard error, and range of quantitative data were determined. The Kolmogorov-Smirnov (KS) test was employed as a normality check. The long non-coding

RNA is up-regulated if the FC is positive and down-regulated if the FC is negative. Numbers and percentages were utilized to present qualitative data, and the chi square (2) test was performed to determine significance. A Spearman correlation was employed to determine the association between GAS5 and the research parameters (SPSS, IBM Corporation), New York). The case differentiation discrimination value GAS5, as well as selection of optimal sensitivity and specificity cut-points could be detected by the receive operating characteristic (ROC) curve. P 0.05 was used to interpret the findings of the significance tests.

Results

35 patients with BD (mean age, 36.1 years; SD = 10.8), divided into 24 men and 11 women (respectively, 68.6% and 31.4%) and 30 healthy controls divided into (22 men and 8 women (respectively, 73.3% and 26.7%)). There were no significant variations in age or sex between the two groups in the current study's participants, who had mean ages of 39.1 years and SDs of 5, respectively (p = 0.146 and 0.674). The demographic and clinical characteristics of BD patients and controls are summarized in Table (2, 3).

Table (2): distribution of age and sex of patients and controls

Variable		**Cases (N =35)**	**Control (N =30)**	**P. value**
Age(years) Mean ± SD		36.1 ± 10.8	39.1± 5	0.146*
Sex N (%)	Female	11 (31.4%)	8 (26.7%)	0.674**
	Male	24 (68.6%)	22 (73.3%)	

*Independent-t test **Chi-squared test

Table (3): Clinical characteristics of BD cases

Variable **mean± SD (range) or n (%)**	**BD patients** **(n= 35)**
Family history of BD	7 (20)
Duration (years)	6.8±6
Manifestations	
Oral ulcers	35 (100)
Genital ulcers	30 (85.7)
Erythema nodosum	16 (45.7)
BDCAF	
0	12 (34.3)
1	12 (34.3)
2	4 (11.4)
3	5 (14.3)
4	1 (2.9)
7	1 (2.9)
Medications	
Azathioprine	30 (85.7)
Biological drug	1 (2.9)
Laboratory investigations	
HB (g/dl)	12.05± 1.49
PLT (10^3 /uL)	244± 55.7
WBC (10^3 /uL)	7.24± 4.16

BDCAF: Behçet's Disease Current Activity Form, HB: hemoglobin, PLT: platelets count, WBC: White Blood Cells count.

The difference in the levels of GAS5 expression in cases and controls was statistically significantly higher in cases (N=35, median =1.98, range: 0.01 to 54.57) than in controls (N=30, median =1, range: 1 to 1) (p-value =0.0001).Table (4)

Table (4): Serum expression level of GAS5 in cases and control

	Cases (N=35)			**Control (N=30)**			**P-value**[#]
	Median	**Range**		**Median**	**Range**		
GAS5	1.98	0.01	54.57	1	1	1	**<0.0001**[*]

#Mann-Whitney U test *Significant

Except for the joint manifestation, where there was a substantial rise in GAS5 expression level between cases with joint manifestations (median=3.58, ranged from 0.01 to 54.57), there was not any correlation between GAS5 expression level and the characteristics of BD patients. And contrasted with a normal

joint with a median of 1.13 (ranging from 0.07 to 31.34), where P-value was 0.028 Table (5).

Table (5): Relation between GAS5 expression and clinical characteristics of BD patients

		GAS5			P-value
		Median	Range		
Sex	Female	4.20	0.52	51.07	0.133#
	Male	1.13	0.01	54.57	
Family H/O	Negative	1.42	0.01	54.57	0.531#
	Positive	4.5	0.56	30.23	
Genital ulcer	Absent	1.04	0.52	30.23	0.448#
	Present	2.04	0.01	54.57	
Cutaneous Lesions	Absent	1.98	0.01	54.57	0.502#
	Erythema nodosum	1.62	0.07	31.34	
Activity	No	1.12	0.07	51.07	0.440#
	Yes	2.1	0.01	54.57	
BDCAI	0	1.12	0.07	51.07	0.145##
	1	1.6	0.01	30.23	
	2	20.84	4.5	54.57	
	3	1.63	0.07	34.66	
	4	0.56	0.56	0.56	
	7	31.34	31.34	31.34	
Fundus Ex	Normal	2.1	0.01	54.57	0.832#
	Uveitis	1.8	0.07	34.66	
Vascular	Positive	4.61	1.04	34.66	0.171#
	Negative	1.42	0.01	54.57	
pathergy test	Negative	2.97	0.13	54.57	0.359#
	Positive	1.56	0.01	51.07	
Joint manifestations	positive	3.58	0.01	54.57	**0.028#***
	Negative	1.13	0.07	31.34	
CNS	Headache	3.58	1.11	31.34	0.384##
	CVS	1.22	0.52	31.34	
	NAD	1.13	0.01	54.57	

BDCAF: Behçet's Disease Current Activity Form #Mann-Whitney U test ## Kruskal-Wallis test

*Significant

The Correlation between GAS5 and other biochemical parameters showed that there was not any correlation between GAS5 and other biochemical parameters as shown in **Table (6).**

Table (6): Correlation between GAS5 level and other biochemical parameter

Group / Parameter	Behçet's disease group N = 35	
	GAS 5	
	Correlation coefficient (r)	P. value
WBCs	-0.077	0.66
PLT	0.030	0.866
HB	-0.032	0.856

HB: hemoglobin, PLT: platelets count, WBC: White Blood Cells count,
** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

To determine the diagnostic utility of GAS5expression levels across all BD patients and healthy controls, ROC curve studies were also carried out. Figure (2) and Table (7) show an illustration of the ROC curve. GAS5 level was found to be useful in distinguishing BD from healthy controls. The AUC for GAS5 expression was 0.743 (95% confidence interval (CI): 0.598-0.888; sensitivity was 74.3, and specificity was 100 %. Our findings suggested that the amount of GAS5 expression may represent viable indicators for the diagnosis of BD.

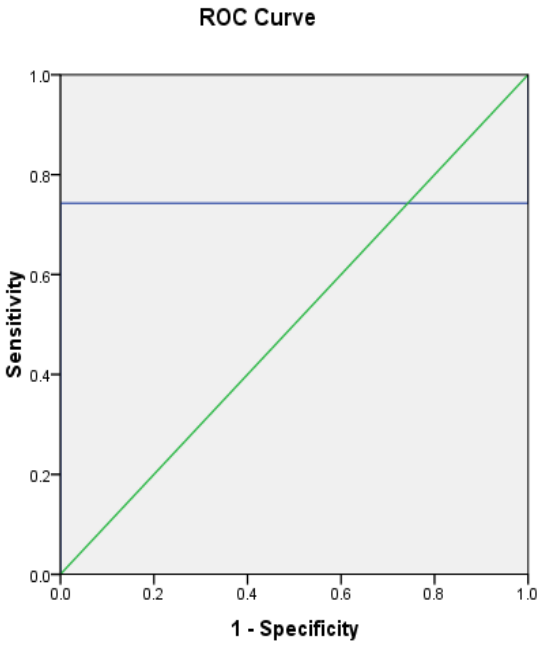

Fig.(2): ROC curve for detecting BD using GAS5.

Table (7): Area under the curve of ROC curve for GAS5 in patient group.

Variable	AUC 95% CI	P-value	Cut-off point	Sensitivity	Specificity
GAS5	0.743 (0.598-888)	**0.001***	1.02	74.3	100.0

Discussion

Recurrent oral aphthous ulcers, vaginal ulcerations, ocular symptoms, and other systemic involvement are hallmarks of Behçet's disease **(Bettiol *et al*., 2020).** The clinical signs and symptoms of BD vary by nation, geography, and ethnicity. Some factors like gender and age upon onset, have found to affect clinical aspects of Behçet's disease and the human leukocyte antigen (HLA)-B51 also have been observed to influence them. Although the condition is frequently diagnosed in people in their third and fourth decades, it can also occur in those over 50 or in children. Although BD affects both sexes equally, guys typically experience a more severe course. Genital ulcers and erythema nodosum are more prevalent in women, but ocular symptoms, vascular lesions, and pustular lesions are more severe in men **(Bang *et al*., 2013).**

Molecules longer than 200 nucleotides are known as long non-coding RNAs (LncRNAs) **(Tano *et al*., 2012).** A variety of biological processes were actively regulated by LncRNAs, including the development and function of immune cells. Recent research has revealed that LncRNAs are involved in the etiology of rheumatic diseases as SS, SLE, and RA **(Li *et al*., 2018).**

A transcript specific to human growth arrest is called GAS5. One LncRNAs, a multi-snoRNA host gene on chromosome 1q25.1, has a small open reading frame, 12 exons, and 11 introns that encode the same 10 snoRNAs (ORF). It is considered not have the ability for proteins encoding and is instead spliced into two mature LncRNAs, known as GAS5a and GAS5b because alternative 5′- splice donor sites in exon 7 **(Smith *et al*.,1998).**

Mature GAS5, is a 630 nucleotide in length, long LncRNAs transcript that was crudely extracted from a subtraction cDNA library of growth-arrested cells that was primarily discovered to function as a tumor suppressor in human cancer. While GAS5 expression may be controlled at the transcriptional level in differentiating cells, saturating cell density or food shortage can raise GAS5 levels and cause growth to stop at the post-transcriptional level **(Fleming *et al*., 1998).** The most likely understood process is the former process, which required collaboration between the nonsense-mediated decay (NMD) and mammalian target of rapamycin (mTOR) pathways, **(Tani *et al*.,2013)**The mTOR pathway selectively regulates the translation of the 5′-terminal oligopyrimidine RNA GAS5 **(Mourtada *et al*., 2010).** NMD has

previously been recognized as an RNA quality control mechanism to get rid of aberrant transcripts and manage GAS5 activity in mammalian cells **(Tani *et al*., 2013).**

The current study suggested to determine the amount of expression level of the genes for growth arrest-specific 5 (GAS5) in Behçet's level illness, an autoimmune condition, and to correlate that with clinical features.

The present study found that serum GAS5 expression level was up regulated ($P < 0.0001$) among cases than controls, that agreed with Mahmoud *et al*., (2020) who proved that serum GAS5 expression level was up regulated in MS (multiple sclerosis) patients as compared to those of healthy controls **(Mahmoud *et al*., 2020).** This refers to that GAS5 is a downstream target of mTOR in T-cells, the GAS5 up regulation could be referred to mTOR activation in T cells during MS. Notably, mTOR inhibitors exerted beneficial effects in different MS experimental models by reducing T-cell activation, increasing T-regulatory cell function as well as modulating glial responses **(Mammana *et al*., 2018).**

Current study discovered that patients with BD had considerably higher expression levels of GAS5 than did healthy donors ($P 0.0001$). Our findings suggested that increased GAS5 expression was unique to BD and that GAS5 might play a role in the etiology of BD. It was in line with the findings of **Qi-Feng Suo *et al.*, (2017),** who discovered that GAS5 expression was identified in each of these group pair sets and that patients with SLE had greater GAS5 levels in relation to ulceration (higher in those with ulceration than in those without ulceration) . On contrast, Olfat *et al.*, (2020) showed that the mean GAS5 was significantly higher in the control that was in disagreement with our results **(Olfat *et al*., 2020)**

Moreover, Manal *et al*., (2021) demonstrated that SLE patients' GAS5 levels were lower than those of controls. **(Manal *et al*., 2021).** With a p value of 0.028, there was a significant connection between GAS5 and joint symptoms. No associations between GAS5 and other clinical information were found.

Limitation that should be put in consideration, the relatively small sample size therefore, further studies with large samples in other ethnic groups are required particularly to study and explain the correlation between these markers and different clinical data in BD.

Conclusion: GAS5 was differentially expressed in serum of BD patients and it had a potential diagnostic value for the detection of the disease.

Conflict of interest: none

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دور تعبيرالحمض النووي الطوِيل الغير مشفر الخاص بتوقف النمو 5 (GAS5) في المرضى المصريين المصابين بمرض بهجت

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مرض بهجت هو حالة التهابية مزمنة تتكرر وتتسم بتقرحات في الفم والمهبل ، وأعراض على العين ، وتأثيرات جهازية أخرى.
كانت الدراسة تهدف الي تقييم دور التعبير الخاص بالحمض النووي الطويل الغير مشفر Gas5 في تطور مرض بهجت.
شملت هذه الدراسة علي 35 مريضا مصابا بمرض بهجت (24 من الذكور و 11 من الاناث) ,30 شخص من الاصحاء (22 من الذكور و 8 من الاناث). تم فصل العينات وحفظ الامصال وتخزينها في درجة حرارة -80 درجة مئوية حتي وقت التحليل. تم استخدام هذه الامصال في استخلاص الجين قيد الدراسة (Gas5) باستخدام ال PCR.
عند مقارنة الحالات بالضوابط ، كان هناك ارتفاع ذو دلالة إحصائية في تعبير GAS5 P. Value 0.0001). مع AUC قدره 0.743 (95 ٪ فاصل الثقة (0.598-0.888 :(CI ؛ الحساسية = 74.3 ، الخصوصية = 100٪) ، أظهر منحنى ROC أن Lnc RNAs مفيدة في تمييز BD من الضوابط الصحية)
أثبتت هذه الدراسة أن Lnc RNA GAS5 يمكن اعتباره علامة بيولوجية تشخيصية جديدة لمرض بهجت.