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Original Article

Analysis of *G3BP1* and *VEZT* Expression in Gastric Cancer and Their Possible Correlation with Tumor Clinicopathological Factors

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: This study aimed to analyze *G3BP1* and *VEZT* expression profiles in patients with gastric cancer, and examine the possible relationship between the expressions of each gene and clinicopathological factors.
Materials and Methods: Expression of these genes in formalin-fixed paraffin embedded (FFPE) tissues, collected from 40 patients with gastric cancer and 40 healthy controls, was analyzed. Differences in gene expression among patient and normal samples were identified using the GraphPad Prism 5 software. For the analysis of real-time polymerase chain reaction products, GelQuantNET software was used.
Results: Our findings demonstrated that both *VEZT* and *G3BP1* mRNA expression levels were downregulated in gastric cancer samples compared with those in the normal controls. No significant relationship was found between the expression of these genes and gender (P-value, 0.4835 vs. 0.6350), but there were significant changes associated with age (P-value, 0.0004 vs. 0.0001) and stage of disease (P-value, 0.0019 vs. 0.0001). In addition, there was a direct relationship between *VEZT* gene expression and metastasis (P-value, 0.0462), in contrast to *G3BP1* that did not demonstrate any significant correlation (P-value, 0.1833).
Conclusions: The results suggest that expression profiling of *VEZT* and *G3BP1* can be used for diagnosis of gastric cancer, and specifically, *VEZT* gene could be considered as a biomarker for the detection of gastric cancer progression.

Keywords: Stomach neoplasms; *G3BP1*; *VEZT*; Gene expression

INTRODUCTION

Although the incidence of gastric cancer has been dramatically declined due to lifestyle and environmental changes, like *Helicobacter pylori* eradication and smoking cessation, this cancer still remains the 5th most common malignancy in the world. Moreover, it is the third leading cause of cancer-related death in both sexes worldwide [1]; in 2011, it accounted for 4% of cancer death [2]. The distribution of gastric cancer varies across geographical regions, which illustrates the multitude of factors that are associated with the incidence, survival, and mortality rates of the disease [3]; even marital status, low educational attainment, and low income increase the risk of gastric cancer [4]. In 2012, 70% of gastric cancer cases occurred

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in developing countries, and about half of them occurred in eastern Asia [3,5]. Similar to other cancers, epigenetic changes, including DNA methylation, epigenetic gene silencing, and histone modifications play a key role in the development of gastric cancer [6].

As classified by Laurén, the 2 main histologic subtypes of gastric cancer are intestinal and diffuse type, which are different in molecular profiles, epidemiology, etiology, pathogenesis, and behavior of the disease [1,7]. For example, the intestinal gastric cancer commonly arises from a premalignant gastric change, such as atrophic gastritis followed by intestinal metaplasia and dysplasia, which in turn, develops into a chronic inflammatory condition that is usually induced by *H. pylori* infection [1,7]. Because of gastric cancer heterogeneous properties [1,7], the identified biomarkers for diagnosis of this disease are rare. There are several molecular markers associated with the early diagnosis of gastric cancer, including the carcinoembryonic antigen, cancer antigen 19-9, and recently, some of microRNAs (miRNAs) and DNA hypomethylation. Other molecular markers, such as growth factors, cytokines, cell cycle regulators, apoptosis-associated factors, and epigenetic alterations are associated with the prognosis of gastric cancer [8].

Modification of downstream or upstream effectors of *Ras* signaling, or activating mutations in *Ras* genes, lead to aberrant activation of *Ras* signaling [9]; this phenomenon has been regularly reported in several types of tumors. *G3BP1* is a downstream effector of *Ras* signaling [10]. Overexpression of G3BP1 protein has been reported in several types of human tumors, such as gastric cancer, colon cancer, head and neck cancers, pancreatic cancer, breast cancer, and esophageal squamous carcinoma [10-15]. G3BP1 protein can bind to various proliferation-related proteins, like RasGAP through its conserved N-terminal nuclear transport factor 2-like domain [10,16-18]. In addition, G3BP1 protein can mediate metabolism of mRNA through its phosphorylation-dependent RNase activity, which originates from its RNA recognition motif [19]. Inactivation of tumor suppressor genes is an essential step in the development of gastric cancer [20,21]. miRNAs and promoter methylation plays a fundamental role in gene inactivation. Particularly, miRNAs regulate the expression of a protein-coding gene, via degrading its mRNA or inhibiting its translation [21]. *VEZT* gene encodes an adherens junctions transmembrane protein, called *VEZATIN*. This protein has 3 domains, extracellular, transmembrane, and intracellular. The intracellular domain of *VEZATIN* is long and binds directly to myosin VIIA [22], while it is indirectly connected with actin cytoskeleton and E-cadherin-catenin complex [23]. Recently, miRNAs and promoter methylation were reported as 2 significant mechanisms of the transcriptional inactivation of genes in human cancer [24]. The *VEZT* gene has been identified as a tumor suppressor gene; therefore, the role of promoter hypermethylation of this gene and miRNAs was analyzed [20,22,24].

In this study, we examined the expression of *G3BP1* gene, which has been suggested to modulate the proliferation, migration, and invasion of gastric cancer tumor cells [10], as well as the expression of *VEZT* gene that has been identified as a tumor suppressor gene [20]. We also analyzed the correlation between the expression of these genes and disease progression, cell differentiation, age, and gender in Iranian patients with gastric cancer.

MATERIALS AND METHODS

In this study, formalin-fixed paraffin embedded (FFPE) samples derived from 2 different patient groups, were used to examine the expression signature of the genes. With the collaboration

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Table 1. Summary statistics for clinical variables among the patient population

Variables	No. of patients
Age (yr)	
≥50	20
<50	20
Chemotherapy	
Yes	40
No	0
Radiation therapy	
Yes	40
No	0
H. pylori	
Patient (+/−)	40/0
Normal (+/−)	0/40
Disease metastasis (M)	
M1	25
M0	15
TNM classification	
I	15
II	8
III	7
IV	10
FFPE	
P	40
N	40

TNM = tumor, node, metastasis; P = patient; N = normal; FFPE = formalin-fixed paraffin embedded.

of government and public sector hospitals, a total of 40 clinical files of patients with gastric cancer from 2014 to 2016, were investigated. In the cascade of genomic and phenotypic changes, which have been described as "multistep oncogenesis," invasive gastric cancer is the last step. This process includes a variety of gradually dedifferentiated phenotypes, which may result in a new cell, characterized by independent and potentially metastatic growth (termed as plasia). The World Health Organization has redefined dysplasia as non-invasive neoplasia. In the natural history of gastric cancer, dysplasia precedes invasive adenocarcinoma. A total of 40 paraffin-embedded tissue samples from patients with gastric cancer and 40 samples from healthy individuals for alternative reasons were selected. The histologic grade is a qualitative assessment of the differentiation of the tumor expressed, as the extent to which a tumor resembles the normal tissue at that site. Tumors with well-differentiated cancer cells are less aggressive than undifferentiated or poorly differentiated cancer cells. In most types of cancer, tumors have moderately differentiated cancer cells; these cells are somewhere between well-differentiated and un-differentiated cells (**Table 1**). Patients who developed recurrent gastric cancer or metastasis, underwent ultrasound, radiography, bone scan, and pathology investigations, and their clinical information were utilized for further analysis. RNA was extracted from FFPE samples and analyzed via real-time reverse transcription polymerase chain reaction (RT-PCR). The study was approved by ethical committee of Deputy of Research Affairs of Shahid Beheshti University of Medical Sciences.

Real-time PCR assay, gene selection, and designing of primers

G3BP1 and *VEZATIN* genes, which were reported to have a significant association with gastric cancer, were selected from gene expression databases [2,5,16,21,25]. The expression level of *G3BP1* and *VEZATIN* genes in tumor and marginal non-tumor samples was investigated via specific *G3BP1* primers, F: 5′-AAACGTTTGTCCTTGCTCCT-3′ and R: 5′-TTCAGACTCCTCCTGAGGCT-3′); and *VEZATIN* primers, F: 5′-ACCGAAGTGATTTCCAGAGG-3′ and R: 5′-AGATGCTGACTTGGATGCTG-3′. Furthermore,

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GAPDH gene was used as an internal control, and its primer sequences were as follow; *GAPDH* F: 5′-ATGGAGAAGGCTGGGGCT-3′ and *GAPDH* R: 5′-ATCTTGAGGCTGTTGTCATACTTCTC-3′. Quantitative real-time PCR was performed using SYBR® Green Master mix (Bio-Rad Laboratories, Inc., Hercules, CA, USA), according the manufacturer's instructions. The PCR program was as follow: initial denaturation at 95°C for 10 minutes, followed by 40 cycles of denaturation at 95°C for 10 seconds, and annealing/extension for 30 seconds at 54.5°C, 58°C, and 59°C for *G3BP1*, *VEZT*, and *GAPDH,* respectively. To minimize experimental variability of the cycle threshold (Ct) values, defined as the cycle number where the fluorescent signal is higher than the background level in the exponential phase of the PCR amplification, those values were determined via the second derivative maximum method. The PCR product size was verified by electrophoresis on agarose gel, and the authenticity of amplified fragment was confirmed via direct sequencing of the PCR product.

RNA extraction

After paraffin removal stage using xylene, tissue digestion was performed by proteinase K (Fermentas, Waltham, MA, USA). Then, the total RNA was isolated using RNX-Plus (SinaClon, Karaj, Iran), according to the protocol supplied by the manufacturer (CinnaGen Co., Tehran, Iran) [26]. Quality assessment of the total RNA was established using NanoDrop 2000 (Thermo Fisher Scientific, Wilmington, DE, USA). After RNA isolation using RNeasy® Kit (Applied Biosystems, Foster City, CA, USA), the RNA quality was assessed using Agilent RNA 6000 Nano Kit (Agilent Technologies, Santa Clara, CA, USA). Total RNA extracted from the tissue section was reverse transcribed in a reaction mixture containing 250 mM Tris-HCl buffer (pH 8.3; 375 mM KCl and 15 mM $MgCl_2$) (Applied Biosystems), 0.1 MDTT (Applied Biosystems), 10 mM dNTPs (Fermentas), 20 U/reaction of RNasin™ ribonuclease inhibitor (Applied Biosystems), and 200 U/reaction of Superscript™ III RT (Applied Biosystems). The cDNA obtained, was diluted by 10-fold in 2 ng/μL polyinosinic acid, and used in quantitative PCR (qPCR) reactions [26].

Real-time qPCR

The qPCR reactions were performed in 96-well plates on a real-time PCR 7500 (Applied Biosystems) instrument. Typically, a total 20 μL of the reaction mixture contained 100 ng of cDNA, 12.5 μL of assays-on-demand SYBR Green PCR Master Mix (Applied Biosystems), of these genes were used, 1 μL each of 10 mmol/μL forward and reverse primers, and 4.5 μL nuclease-free water. All PCRs were performed using the ABI Prism 7500 System (Applied Biosystems) under the conditions recommended by the manufacturers. A standard curve was constructed with at least 4 different concentrations in triplicate, using a control cDNA for both the control gene (*GAPDH*) and the genes of interest. These 2 genes were analyzed in 40 paraffin-embedded tissue. Differences in gene expression among metastatic and normal samples were estimated using Student GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA) with the t-test analysis. The relative gene expression levels were determined using the comparative Ct (ΔΔCt) method. Another analysis was performed using the GelQuantNET software (BiochemLabSolutions, San Francisco, CA, USA) to examine the real-time RT-PCR products.

RESULTS

To examine whether *G3BP1* and *VEZT* expression levels are correlated with clinicopathological factors of patients with gastric cancer, *G3BP1* and *VEZT* expression levels were evaluated in gastric cancer and normal specimens; *GAPDH* gene expression was used as internal control.

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To analyze the specificity of qPCR products and absence of unspecific PCR products and dimer primers, the melt curves of each gene were drawn, independently (**Fig. 1**).

After converting the calculated Ct for each sample to relative quantitation (RQ), gene expression was assessed via the ΔΔCt method. Expression of each gene was compared between normal and cancerous samples. A graph for each gene was generated, independently.

Analysis of both *G3BP1* and *VEZT* expression levels and clinicopathological variables was performed via the t-test. We analyzed the correlation between expression of each of *G3BP1* and *VEZT* genes, individually, with clinicopathological factors in patients with gastric cancer. A summary of the results is presented in **Table 2**.

All cancerous samples showed a decrease in mRNA expression level of *VEZT* compared with the normal samples. Correlation between mean RQ of *VEZT* in patients lower than 50 years-old and above 50 years-old was significant (P-value, 0.0001). Similarly, there was a significant

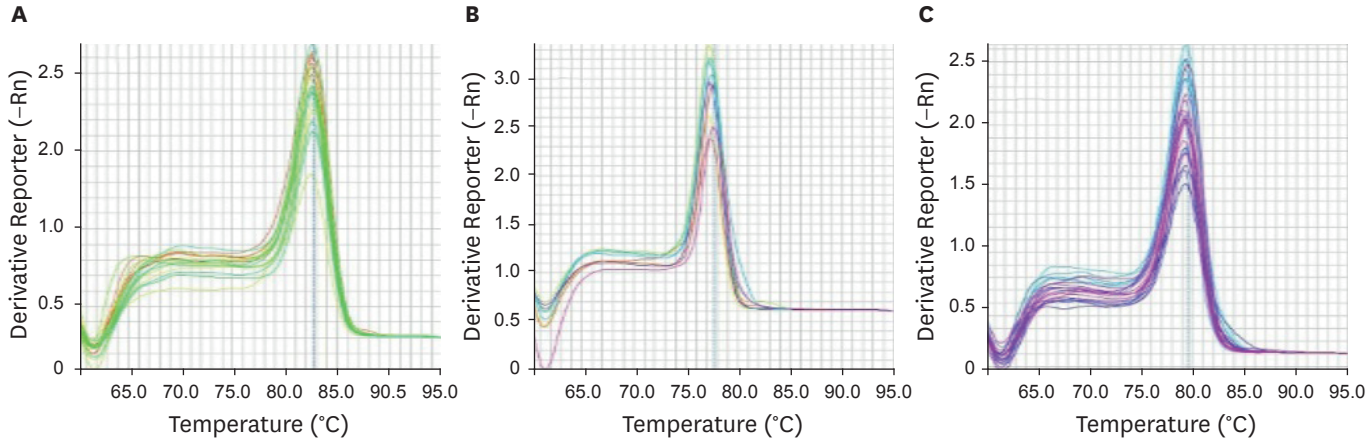

Fig. 1. Melting curves of (A) *GAPDH*, (B) *VEZT*, and (C) *G3BP1* genes in normal and cancerous samples show specific qPCR products for each gene.
qPCR = quantitative polymerase chain reaction.

Table 2. Correlation of *G3BP1* and *VEZT* expression with clinicopathological factors in patients with gastric cancer

Variables	No.	*G3BP1* mean RQ	*VEZT* mean RQ	*G3BP1* P-value	*VEZT* P-value
Samples				0.6344	0.0004
Patients	40	0.9308	0.4322		
Normal	40	1.0116	1.0292		
Gender				0.4835	0.6350
Male	21	0.8861	0.5247		
Female	19	0.9783	0.4737		
Age (yr)				0.0004	0.0001
<50	20	1.1909	0.4402		
≥50	20	0.7961	0.7885		
TNM Classification				0.0001	0.0019
I	15	0.8883	0.4204		
II	8	0.6687	0.4534		
III	7	0.3655	0.2667		
IV	10	0.1603	0.1334		
Disease metastasis (M) *G3BP1* and *VEZT*				0.1833	0.0462
M1	25	0.6606	0.4308		
M0	15	0.8735	0.6540		

RQ = relative quantitation; TNM = tumor, node, metastasis.

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relationship between the stage of the disease, metastasis, and gene expression (P-value, 0.0019 and 0.0462). However, no significant relationship was observed between gender and *VEZT* gene expression (P-value, 0.6350).

Although the expression of *G3BP1* mRNA level in most of gastric cancer samples were downregulated, our analysis showed no significant correlation between *G3BP1* expression and gender and disease metastasis (**Table 2**). As it is shown in **Fig. 2**, there is a significant relation between *G3BP1* gene expression and the disease stage.

After electrophoresis and imaging of the qPCR products, the findings were analyzed using GelQuantNET software (BiochemLabSolutions; **Fig. 3**). Again, the only significant relationship was related to the stage of disease and down-regulation of *VEZT* gene, and all the results were consistent with the qPCR results.

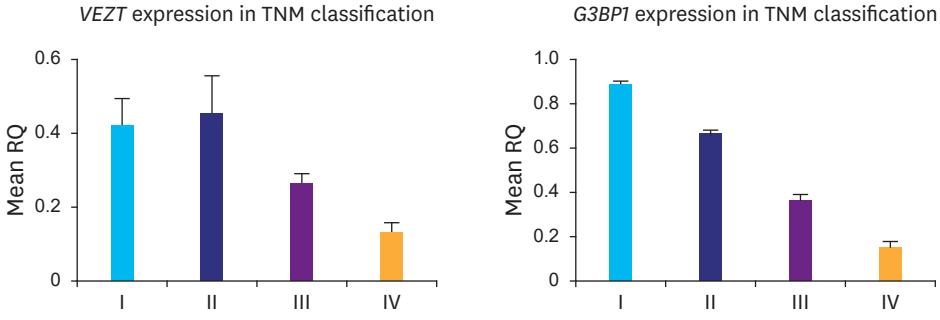

Fig. 2. *VEZT* and *G3BP1* gene expression mRNA level in TNM calssification.
The achieved results were analyzed with GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA). Each experiment was repeated 3 times. The P-value for *VEZT* and *G3BPI* are 0.0019 and 0.0001, respectively.
TNM = tumor, node, metastasis; RQ = relative quantitation.

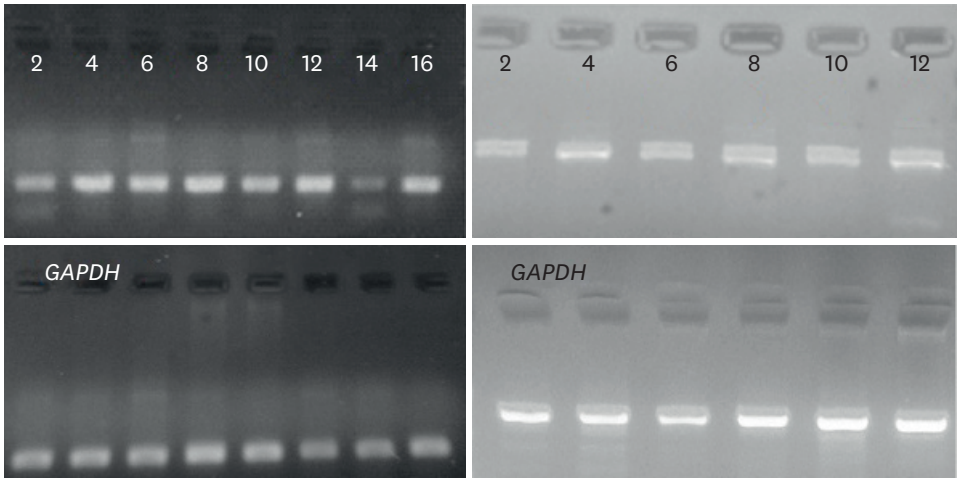

Fig. 3. *G3BP1* and *GAPDH* real-time PCR products were loaded in upper and lower lane, respectively. The results obtained after GelQuantNET software (BiochemLabSolutions, San Francisco, CA, USA) and GraphPad Prism 5 analysis (GraphPad Software, Inc., La Jolla, CA, USA), suggest no significant correlation between the *G3BP1* expression and disease progression (P-value, 0.0886), while *VEZT* expression was found to be significantly correlated (P-value, 0.0175).
PCR = polymerase chain reaction.

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DISCUSSION

Gastric cancer is the second most common cancer in the world. It is now obvious that various genetic alterations, including *H. pylori* infection, activation of oncogenes, and inactivation of tumor suppressor genes, are necessary stages in gastric cancer development [20]. Studies have shown that people who carry high-risk genetic variants and have specific dietary habits can have an increased risk of gastric cancer, compared with those who do not carry high-risk genetic variants, which may justify the higher incidence rates of gastric cancer in specific countries [27]. *VEZT* and *G3BP1* genes are 2 biomarkers, which their expression in gastric cancer tumors was evaluated, separately.

Modification of *G3BP1*, as a downstream effector of *Ras*, can cause aberrant activation of *Ras* signaling, which has been reported in various types of tumors [9]. The significant role of *G3BP1* in promotion of proliferation, migration, invasion, and survival of tumor cells has been also reported in several studies [10]. A previous study demonstrated up-regulation of *G3BP1* at the post-transcriptional level in gastric cancer tumors, although in most gastric cancer cases the mRNA levels were decreased [10]. Another study demonstrated that activation of the heregulin-human epidermal growth factor receptor 2 (HRG-HER2) signaling pathway in breast cancer cells might contribute to the up-regulation of *G3BP1* at the mRNA and protein levels [13]. Molecular and functional studies indicate that the interaction of *G3BP1* with β-F1 mRNA inhibits its translation, supporting a role for *G3BP1* in the glycolytic switch that occurs in cancer [25]. Two previous studies demonstrated that Y-box binding protein 1 regulates a ribonucleoprotein complex, known as stress granules, as well as formation [28,29] and tumor progression by translationally activating *G3BP1*. Moreover, down-regulation of *G3BP1* in sarcoma xenografts, which prevents tumor invasion and blocks lung metastasis in mouse models, has been reported [28]. Finally, inactivation of the p53 tumor suppressor pathway is a critical step in human tumorigenesis and isoforms of *G3BP*, including *G3BP1* and *G3BP2*, were suggested as negative regulators of p53 [30]. In line with a previous study [10], our results showed a decrease in *G3BP1* mRNA expression level of most patients' samples in comparison with the normal samples, but no significant correlation between *G3BP1* mRNA expression level and age, gender, cell differentiation, and cancer stage, was observed.

As previously mentioned, the inactivation of tumor suppressor genes is an essential step in the development of gastric cancer. Promoter hypermethylation of gastric cancer cell lines was demonstrated using methylation specific PCR [24] and bisulfite sequence-PCR methods [20,24]. Moreover, a luciferase reporter assay demonstrated that miR-43c suppresses VEZT protein expression [24]. In another study, epigenetic regulation and biological functions of *VEZT* in gastric cancer tumors were examined, showing that *VEZT* was hypermethylated in tissues and blood of patients with gastric cancer compared with those of healthy controls. Additionally, *H. pylori* was reported as an inducing factor of methylation and silencing of *VEZT* gene in GES-1 cells, since promoter methylation of *VEZT* in *H. pylori* positive patients was 2.4-fold higher than in the healthy controls [20]. Although the correlation between expression of *VEZT* and age, gender, cell differentiation, tumor size, and tumor site were not reported, a significant association was observed with lymphatic metastasis, tumor, node, metastasis (TNM) stage, depth of cancer, and longer overall survival [20,22]. Inhibition of cell proliferation, migration, invasion, and tumorigenesis in vivo and in vitro via *VEZT* expression restoration in gastric cancer cell lines, suggests that *VEZT* can be considered as a therapeutic agent in the treatment of gastric and/or other cancers [20,22,24].

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Similar to the previous studies [20,22] the genetic variation in different populations, as well as the role of epigenetic factors and the single nucleotide polymorphisms, demonstrate the need of similar studies of *VEZT* and *G3BP1* genes in patients with gastric cancer in the Iranian population; for this reason, this study investigated the expression levels of these genes in samples from Iranian individuals. Our results showed that *VEZT* mRNA levels were decreased in all gastric cancer samples and expression of this gene had a significant correlation with the status of gastric cancer progression. Therefore, evaluation of *VEZT* and *G3BP1* gene expression could be used as a molecular technique for diagnosis of gastric cancer. Finally, this study suggests that *VEZT* gene could be considered as a biomarker for detection of gastric cancer progression.

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