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ORIGINAL ARTICLE

Identification of Genes Involved in Prostate Cancer Based on Gene Expression Profiles

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ABSTRACT

Background: Prostate cancer is a disease of increased prevalence, which is associated with high mortality. The lack of chemo and radiation therapy methods in the advanced forms of this cancer necessitates the investigation of new solutions to control this disease. Prostate cancer is directly associated with changes in the gene expression profiles among the prostate epithelial cells. Therefore, gene expression profiling in prostate tissue will greatly help the early detection of cancer and implementation of appropriate therapeutic interventions. In this study, we examined the gene expression profile of prostate cancer patients and introduced the most important genes affecting the incidence of this cancer.

Materials and Methods: This study was based on the data previously used on prostate gene expression. The data set included 136 samples and a set of 22,283 genes analyzed using the binary regression model and Bayesian gene selection.

Results: In this study, 10 genes were identified to affect prostate cancer. These genes included heat shock transcription factor 2, lipin-1, lymphocyte-specific protein tyrosine kinase, collagen type VI, acid phosphate, ciplation resistance associated, CCAAT/enhancer binding protein beta, folate hydrolase 1 (prostate-specific membrane antigen), inositol polyphosphate 4, and interleukin-1.

Conclusion: As the findings indicated, we can classify the individuals in groups with or without prostate cancer using the gene expression profiles.

Key Words: Bayesian, Gene expression, Prostate cancer

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INTRODUCTION

Prostate is a gland located below the bladder and covers the membranous part of the urethra [1]. Prostate cancer is the third leading cause of death after lung and gastric cancers. This disease is also the second leading cause of mortality in men. In the developed countries, prostate cancer is the second most common cancer after skin cancer and the second most fatal cancer after lung cancer.

According to the statistics, one per six men suffer from this type of cancer [2]. In the United States, about 238,590 and 233,000 new cases of prostate cancer were reported to occur in 2013 and 2014, respectively, resulting in 29,720 deceases [3, 4]. Prostate cancer is more prevalent in Africa; on the other hand, it is less common among the Asian population [5]. This disease is the most prevalent diagnosed cancer among the American males [6]. Hereditary factors account for 10% of the cases [7], indicating the effect of genetic factors on the development and progression of this cancer.

Prostate cancer is caused by the presence of cancer cells in the prostate, which is resulted from the elevation of androgens and leads to urinary tract obstruction. Furthermore, increased testosterone secretion accelerates the malignant progression of prostate cancer. A positive family history is an important factor in susceptibility to this cancer [8].

Genes coding for hormones plays an important role in the creation of this disease. In this regard, mutations in any of these genes have a direct relationship with an increased risk of prostate cancer [9]. Given the growing prevalence and mortality of prostate cancer and the lack of chemo and radiation therapy methods in the advanced forms of this disease, we need

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new solutions to control this disease.

The serum prostate-specific antigen (PSA) level was used as a diagnostic tool for the first time to identify many tumors in the asymptomatic stage. The PSA is a glycoprotein that can rise in benign prostatic hyperplasia and prostate massage; therefore, it cannot be used as a special marker to diagnose prostate cancer [10].

On the other hand, one of the main problems in controlling the prostate cancer is the lack of reliable genetic markers to predict the course of disease and classify its stages. Complete human genome sequence has provided the basis for the gene expression profile of a disease. Since prostate cancer is directly and indirectly associated with changes in the gene expression profile of the prostate epithelial cells, the study of gene expression profile in the prostate tissue will greatly help the early diagnosis and appropriate management of prostate cancer.

In this study, we examined the gene expression profile of the patients with prostate cancer and introduced the most important genes affecting the incidence of this cancer.

MATERIALS AND METHODS

Data

In order to identify the genes involved in prostate cancer, we used the data published previously [11]. For the purpose of the study, we analyzed the gene expression data sets of 148 patients. In these data, the tumor percentage of 12 samples was not reported. The tumor percentages of 71 and 65 samples were 0% and 0.1-0.8%, respectively. The level of gene expression was measure using the Affymetrix arrays on platform U133A.

The data were loaded from the Gene Expression Omnibus database. After sending the data to sites and selection of the Robust Multichip Average (RMA) algorithm, the gene expression data were normalized. The KEGG database contains 22,283 probes.

Statistical Analysis

The data were normalized using the RMA algorithm. This algorithm performs background modification, logarithm to base 2, and normalization based on quantiles on the raw data or colors intensity values. At the end, a linear model was fit to the normalized data to achieve expression values for each probe set on the array [12]. Then, the data were analyzed using the Matlab software version 8.5.

Data analysis was performed using the probit regression model and Bayesian gene selection. The risk classification for each event in every sample was made on gene expression levels by the probit regression model.

RESULTS

Gene expression profiles were analyzed using the probit regression model and Bayesian gene selection. The important genes causing cancer and their numbers are shown in Table 1.

DISCUSSION

In this study, we provided a tool for the recognition of effective factors in the prevention and treatment of prostate cancer by selecting the genes affecting the cancer prevalence. In this regard, ten genes involved in the prostate cancer were identified. These genes included heat shock transcription factor 2, lipin-1, lymphocyte-specific protein tyrosine kinase, collagen type VI, acid phosphatase, ciplation resistance associated, CCAAT/enhancer binding protein beta, folate hydrolase 1 (prostate-specific membrane antigen), inositol polyphosphate 4, and interleukin-1.

The importance of some of these genes has been approved by other methods. Collagen type VI as a gene playing role in human prostate nodular hyperplasia was introduced cells is largely decreased, leading to a sharp by de Carvalho et al. [13]. The expression of collagen type VI gene in human prostate cancer

Table 1. Number and name of important genes in prostate cancer

Number of gene	Name of gene	Comments
11199	211220_s_at	Heat shock transcription factor 2
12198	212272_at	Lipin-1
4957	204890_s_at	Lymphocyte-specific protein tyrosine kinase
16814	216904_at	Collagen type VI
18699	218795_at	Acid phosphatase
8870	208835_s_t	Ciplation resistance associated
12426	212501_at	CCAAT/enhancer binding proteinbeta
5927	205860_x_at	Folate hydrolase 1 (prostate -specific membrane antigen)
8405	208364_at	Inositol polyphosphate 4
13737	213817_at	Interleukin-1

reduction in cell integrity, causing cancer [14]. Prostate specific membrane antigen is significantly increased in prostate cancer cells [15].

Interleukin-1 is reduced among different prostate cancer cell lines, while there is an increase in interleukin-2 antigen [16]. Targeting testicular nuclear receptor 4-interleukin-1 can reduce drug resistance in prostate cancer [17]. Tyrosin kinase gene is involved in prostate cancer [18]. The expression level of heat shock transcription factor 1 gene in prostate cancer is high [19]. Lipin-1 was reported to be over-expressed in 50% of high degree prostate cancer [20].

Lysophosphatidic acid and phosphatase 6 play a role in the progression of prostate cancer [21]. Chronic inflammation has an induction role in the over-expression of CCAAT/enhancer binding protein beta in prostate epithelium, which in turn is associated with increased expression of Cyclo-oxygenase-2 inhibitors and restrain of retinoic acid [22].

CONCLUSION

As the findings of the present study indicated, we can classify the individuals in groups with or without prostate cancer using the gene expression profiles.

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CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

REFERENCES

1. Zabkowski T. Finasteride in the treatment of benign prostatic hyperplasia. Urol A. 2012;51(7):982-6.
2. Carter HB, Partin AW. Diagnosis and staging of prostate cancer. Campbell Urol. 2002; 3:2519-37.
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63(1):11–30.
4. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64(1):9–29.
5. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. Family history and the risk of prostate cancer. Prostate. 1990; 17(4):337-47.
6. Jones J, Grizzle W, Wang H, Yates C. MicroRNAs that affect prostate cancer: emphasis on prostate cancer in African Americans. Biotech Histochem. 2013; 88(7):410–24.
7. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer statistics, 2005. CA Cancer J Clin. 2005; 55(1):10-30.
8. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined cancer is increased through prostate-specific antigen-based screening. JAMA. 1993; 270(8):948-54.
9. Sohrabi M, Onsory K, Bakhtiari Tajar M, Aslanbeigi N, Sajjadi S, SalehiSiavashani E, et al. Genetic polymorphisms of CYP2D6 and prostate cancer risk.NCell MolBiotchnolJ. 2012;2(8):97-104.
10. Alapont Alacreu JM, Navarro Rosales S, Budía Alba A, España Furió F, Morera Martínez F, Jiménez Cruz JF. PSA and hK2 in the diagnosis of prostate cancer. Actas Urol Esp. 2008; 32(6):575-88.
11. Wang Y, Xia XQ, Jia Z, Sawyers A, Yao H, Wang-Rodriquez J, et al. In silico estimates of tissue components in surgical samples based on expression profiling data. Cancer Res. 2010;70(16):6448-55.
12. Irizarry RA, Hobbs B, Collin F, Beazer-Barclay YD, Antonellis KJ, Scherf U, et al. Exploration, normalization, and summaries of high density oligonucleotide array probe level data. Biostatistics. 2003;4(2):249-64.
13. de Carvalho HF, Taboga SR, Vilamaior PS. Collagen type VI is a component of the extracellular matrix microfibril network of the prostatic stroma. Tissue Cell. 1997;29(2):163-70.
14. Patrikainen L, Porvari K, Kurkela R, Hirvikoski P, Soini Y, Vihko P. Expression profiling of PC-3 cell line variants and comparison of MIC-1 transcript levels in benign and malignant prostate. Eur J Clin Invest. 2007; 37(2):126-33.
15. Lapidus RG, Tiffany CW, Isaacs JT, Slusher BS. Prostate-specific membrane antigen (PSMA) enzyme activity is elevated in prostate cancer cells. Prostate. 2000; 45(4):350-4.
16. Abdul M, Hoosein N. Differences in the expression and effects of interleukin-1 and -2 on androgen-sensitive and -insensitive human prostate cancer cell lines. Cancer Lett. 2000; 149(1-2):37-42.
17. Yang DR, Ding XF, Luo J, Shan YX, Wang R, Lin SJ, et al. Increased chemosensitivity via targeting testicular nuclear receptor 4 (TR4)-Oct4-interleukin 1 receptor antagonist (IL1Ra) axis in prostate cancer CD133+ stem/progenitor cells to battle prostate cancer. J Biol Chem. 2013;288(23):16476-83.
18. Robinson D, He F, Pretlowt T, Kung HJ. A tyrosine kinase profile of prostate carcinoma.ProcNatl Acad Sci.1996. 93(12):5958-62.
19. Tang D, Khaleque MA, Jones EL, Theriault JR,Li C,Wong WH, et al. Expression of heat shock proteins and heat shock protein messenger ribonucleic acid in human prostate carcinoma in vitro and in tumors in vivo. Cell Stress Chaperones. 2005;10(1):46–58.
20. Brohée L, Demine S, Willems, Arnould T, Colige AC, Deroanne CF. Lipin-1 regulates cancer cell phenotype and is a potential target to potentiate rapamycin treatment. Oncotarget. 2015; 6(13):11264-80.
21. TanakaaM, KishiaY, TakanezawaaY, KakehibY, AokiaJ,Araia H.Prostatic acid phosphatase degrades lysophosphatidic acid in seminal. FEBS Lett. 2004; 571(1-3):197–204.
22. Wang W, Bergh A, Damber JE. Increased expression of CCAAT/enhancer-binding protein beta in

proliferative inflammatory atrophy of the prostate: relation with the expression of COX-2, the androgen receptor, and presence of focal chronic inflammation. Prostate. 2007; 67(11):1238-46.