Nat. Volatiles & Essent. Oils, 2021; 8(6): 5152-5159

NVEO
Natural Volatiles & Essential Oils

Assessment Of HOXB13 MUTATION In Prostate Cancer (Prca)

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Abstract:

Introduction: Carcinoma of the prostate, or Prostate cancer, has a multi genetic factors. HOXB13 is one of this factors ,specifically the G84E gremlin mutation of HOXB13, which is ported on chromosome 17.The role of HOXB13 in the development of prca was researched in this study.

Method: 60 patients diagnosed with prca in addition to 63 controls. People were classified on the report of their age and familial history, the results were classifiedaccording to the genotype, age, family history, aggressive type of prostate cancer and other types (Hum ,2013) of tumors associated with HOXB13 mutation. This study was based in PCR sequencing to determine the attendance of HOXB13 mutation in prca risk.

Result: The HOB13 mutation was found in 70% of men with a familial history of cancer, meaning they had cancer in their family before, and it was found in the majority of men over 60 years old; the variant was found in exon one of HOXB13. The HOXB13 mutation significantly raises the risk of familial prostate cancer with early onset.

Conclusion: Males with a clear family history of prostate carcinoma may benefit from screening for the G84E mutation, which could help identify those who require more frequent prostate cancer screening.

Keywords: Familial Cancer, Genetic mutation, Homeobox, Prostate Cancer

Introduction:

Prostate cancer, often known as Pr ca, is the second most prevalent disease in men and one of the most common tumours worldwide. Because it affects the prostate, a gland in the male reproductive system, it is classified as an adenocarcinoma. The prostate is a gland that is about

the size of a corn kernel and weighs about 11 grammes. It is covered by the prostatic fascia and is found in the pelvis3. In the United States and Africa, prca is more common than in Asia and Europe. Prostate cancer is caused by a number of variables, one of which is advanced age; 90% of cases diagnosed are men over the age of 50.(**Tao** Z, 2015)

Family history with the prostate cancer or breast cancer, race and environmental factors (like diet, kind of work, life style.). Prostate cancer is one of the cancers strongly related to inherited susceptibility; hereditary susceptibility is estimated to explain as much as 40% (**Bambury**,2012).

The homeobox B13 (HOXB13) gene is involved in prostate development and codes for a transcription factor. The G84E variation has been linked to hereditary prostate cancer in some families, according to sequencing studies. The method by which HOXB13 works is unknown, however studying this pathway could help researchers better understand sporadic incidences of prostate cancer.(16).HOX protein has a role in body axis patterning and tissue differentiation of developing embryos and on organogenesis. HOXB13 gene is located on chromosome 17q21-22 9 **(Quinonez** SC, 2014), In the normal case it plays a role on prostate development, but G84E variant (rs138213197) in the HOXB13 result. In this study is done to point out of genotype of HOXB13 mutation and its frequency in prca.

Material and Method:

Patient and controls:

A total of 60 males diagnosed with carcinoma of the prostate admitted in Al- Sadr Teaching hospital in Najaf Governorate. Their ages are between (40 -80) years old.

Addition to 63 men without cancer in the same age category, as a control group. The result was electrophoresed and calcified in tables.

Setting:

This study was done at Al- Sadr Teaching hospital in Najaf Governorate between 23-9-2020 to25-7-2021

Sample collection /storage:

60 blood samples were collected from patients; 63 blood samples were collected as a control. In EDTA tubes, we sterilized the blood of the two gropes. Genetic DNA Mini kit was used to ue, using a pair extract to genomic DNA. The amplification of the gene HOXB13 was done by PCR technique of primerf-5' CGAGCTGGGAGCATTTA-3'andr-5'- ACGACCAAGCATCATCATCCTCAG-3.

PCR condition was as following, 95°C as initial denaturation for 5 minutes .30 cycles of denaturation at 95°C for 30 seconds. Annealing at 60°C or 30 seconds, extension at 72°C for 1 minutes. A final extension at 72°C for 5 minutes.

Statistical analysis:

The sequencing results were analyzed by BEAST (Basic Local Aligned Search Tool). SPSS was used to calculate OR and 95% cls. OR was considered syndicated if OR≥ 1.5.

Results

Demography study:

1- Age

From 60 patients with prostate cancer there were 50 % of cases with HOXB13 mutation (30 cases) aged from 61-75 years, while only 15 % (9 cases) with HOXB13 mutation aged from 45-60 years. (Table 1, Figure 1)

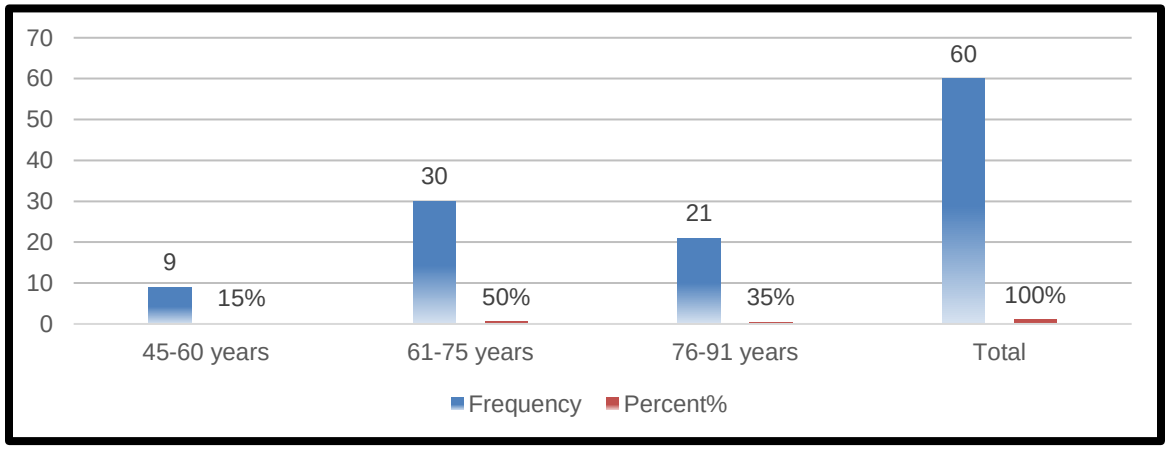


Figure 1: Frequent of HOXB13 in patients with prostate cancer according to age.

Table1: Frequenct of HOXB13 in patients with prostate cancer according to age.

Age	Frequency	Percent%
45-60 years	**9**	**15%**
61-75 years	**30**	**50%**
76-91 years	**21**	**35%**
Total	**60**	**100%**

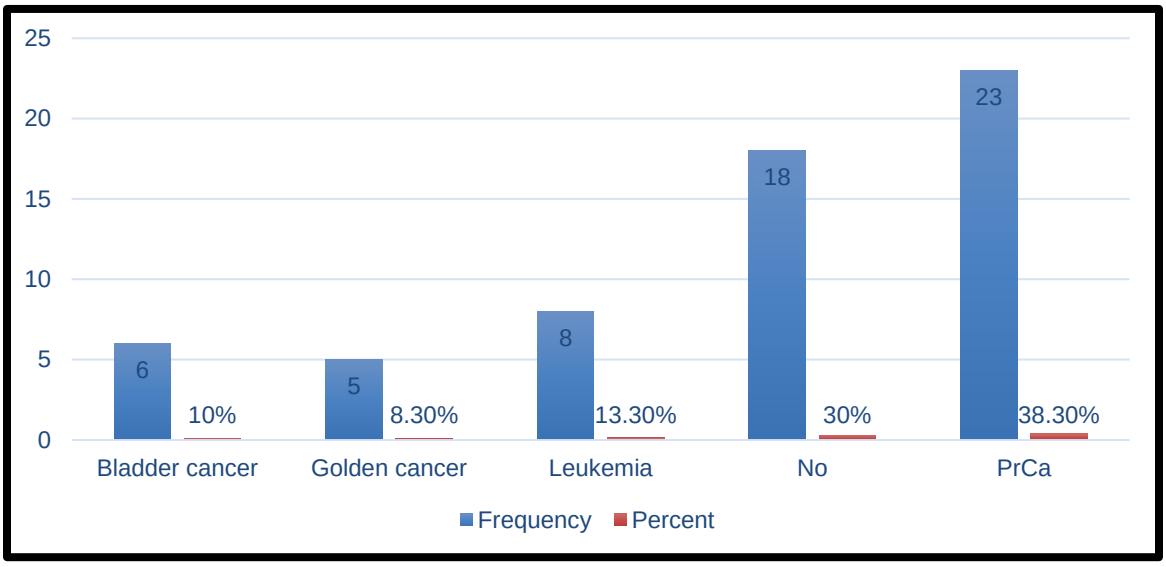
2- Family history

This study showed that the majority of HOXB13 gene mutation was detected in most cases (23 cases) with family history of prostate cancer (38.3%) and also it's detection was observed in rest cases with family history of other types of cancer such as: Urinary bladder cancer (10 %-6 cases), colon cancer (8.3%-5 cases), leukemia (13.3%-8 cases), and even HOXB13 mutation was detected in 18 cases of prostate cancer with no previous family history. (Table

Table 2: Frequency of HOXB13 in patients with prostate cancer according to family history.

Family history genotype	Frequency	Percent
Bladder cancer	6	10%
Golden cancer	5	8.3%
Leukemia	8	13.3%
No	18	30%

PrCa	23	38.3%
Total	**60**	**100%**



3- Type of prca

70 % (42 cases) of cases with prostate cancer were aggressive type while 30 % were non aggressive type. (Table 3)

Table 3: classification of cases according to aggressive type of prostate cancer

Type of PrCa	Frequency	Percent
Aggressive	42	70%
No Aggressive	18	30%
Total	**60**	**100%**

Figure 3: Distribution of snps between patients and controls:

4-**Other tumor in cases**

43.3 % of cases with prostate cancer have no other types of cancer, while 33% had leukemia and prostate cancer and 21.7 % of cases had also bladder cancer with prostate cancer. (table 4)

Table 4: frequency of other tumor in cases with prostate cancer

Other tumor in cases	**Frequency**	**Percent**
Bladder cancer	**13**	**21.7%**
Golden cancer	**1**	**1.7%**
Leukemia	**20**	**33.3%**

No	**26**	**43.3%**
Total	**60**	**100%**

4- DNA sequencing result:

The mutation was detected in exon one. It found that AG polymorphism rs9900627 snps improved the risk of prostate cancer. snps results were presented on(figure3), we conclude that patients with one snps were relevant to develop prca. Using 2% agarose gel electrophoresis as shown on (figure4). The product of five samples were between 500 bp and 1000 bp. The product size is 90.

Snps	Patients	Controls	OR	95% CL
Wild	**19**	**25**	**1**	**----------**
Three snps	**00**	**00**	**----------**	**----------**
Two snps	**09**	**11**	**1.14**	**0.419-3.158**
One snps	**33**	**26**	**1.73**	**0.636-3.700**

OR:odds ratio 95%CL:confidence interval.

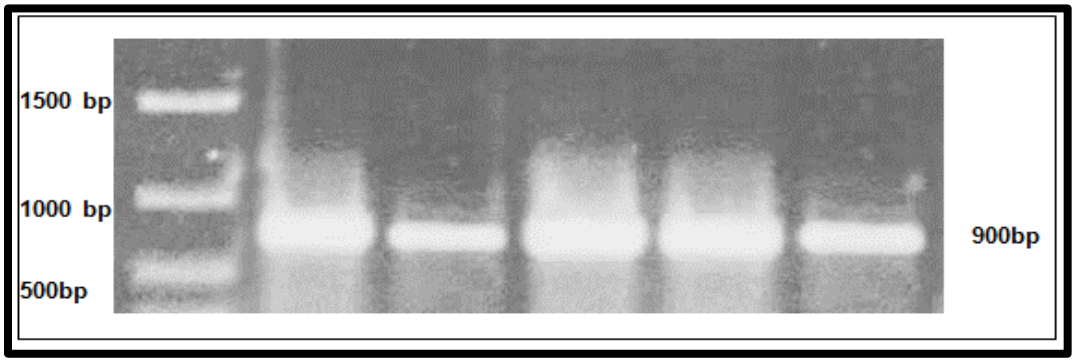


Figure 4: Agarose electrophoresis for PCR Product of HOXB13 gene.

Discussion:

The second most common malignancy in males is prostate cancer. It can be random, just like other malignancies. Prostate cancer is hereditary in 10% of cases, meaning it is carried down to offspring due to a gene mutation. (**Sanjeev Kaul**, 2019).

HOXB13 gene gives instruction to produce a protein, which has a role of regulation[7].The HOXB13 gene is called a Transcription factor according to its role[8].HOXB13 gene mutation is strongly relatedand increase the risk of aggressive prca(**Miyamoto) (Huang** H, 2013) (**Bray** F,2018). Our study was to pick out the effect and the relation between HOXB13 mutation and prostate adenocarcinoma.

Although the genetic reason for this link is unknown, family history is a substantial risk factor for prostate cancer. According to linkage analysis, chromosome 17q21-22 could be home to a prostate cancer genetic component.(**Ewing** CM,2012)Our study agree with this statement as

our result show that 70% cases with family history of cancer were associated with HOXB13 mutation with only 30 % had no previous family history .

New strong connections with bladder cancer and leukaemia have been revealed, highlighting the role of this gene in carcinogenesis **(Beebe-Dimmer** JL,2015).This novel associations agree with our result that 33% had leukemia and prostate cancer and 21.7 % of cases had also bladder cancer with prostate cancer.

The G84E mutation appears to have little effect on the disease's severity. These findings suggest that carriers should be screened more frequently than the overall population, but they should not be treated more aggressively if diagnosed with prostate cancer..(**Witte** JS,2013) In our result :70 % (42 cases)of cases with prostate cancer were aggressive type while 30 % were non aggressive type.

The mutation has been found at chromosome17q-21-22, in exon one. By decoding gremlin DNA, we discovered that certain patients (19) and controls (26) have more than two snps. We reported that patients with one snp were more likely to form prca, OR (1.73), 95 percent CL (0.638-3.700). The result proved relation with environmental and genetic factors like an important factor of prca (**Tao** Z, 2015), (**Shang** Z,2013), (**Clapp RW**, 2008) The mechanisms by which the HOXB13 G84E mutation might act to promote prostate carcinogenesis are unknown **(Thorsteinsdottir** U,2001). Patients with the mutation, which replaces glycine with glutamic acid in codon 84's 2nd position, have a considerably increased risk of prostate cancer than males without the mutated gene.(**C.M. Ewing**, 2012)

Finally, our findings support a link between the HOXB13 G84E variant and prostate cancer, as well as a one-of-a-kind link between G84E and leukaemia and a potential link with bladder cancer

Early-onset, familial prostate cancer is greatly increased by the HOXB13 mutation. Testing for the G84E mutation in individuals with a positive family history of prostate cancer could help determine those who require more annual prostate screening services.

More study is needed to validate these connections and gain a better understanding of the impact of germline HOXB13 mutations in human cancer.

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