UNIVERSITI PUTRA MALAYSIA

SHORT TANDEM REPEATS ON X AND Y CHROMOSOMES IN RELATION TO PROSTATE CANCER RISKS IN SAUDI MALE POPULATION

MOHAMMED HARB KHALIL ALBUJJA

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By

MOHAMMED HARB KHALIL ALBUJJA

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Chairman : Professor Patimah Ismail, PhD
Faculty : Medicine and Health Sciences

Prediction of the susceptible population to any hereditary disease is one of the main tracks of human genetics. Although there were studies related between prostate cancer (PrCa) and family hereditary or Y-chromosome alleles frequencies and other studies related between X-chromosome alleles frequency and PrCa, most of them were inconclusive because of the limited number of biomarkers and/or samples as well as the investigation of sex chromosomes markers separately. Forensic short tandem repeats (STRs) are sometimes best to seek information from lineage markers to aid with specific inheritance scenarios. Therefore, many studies were conducted to establish an association between phenotype and genotype in that disease by Y STR lineages. Lineage markers including Y and X-chromosomes markers can aid kinship analysis. Therefore, in the current study it was hypothesized that the analyses of both X and Y-chromosomes together besides increasing the number of investigated markers to 35 markers (23 in Y-chromosome and 12 in X-chromosome) will give comprehensive linkage information between sex chromosomes and PrCa. Most of the previous studies compare PrCa patients only and healthy controls. Also, they examine the genetic biomarkers on Y-chromosome only. While the current study included PCa and benign prostate hyperplasia (BPH) patients as well as examined the biomarkers on X and Y-chromosomes. Multiple comparisons were done, three of them between (malignant, benign, and malignant plus benign patients), respectively, and healthy controls group. One more comparison was established between benign and malignant patients. This research was carried to fill a gap in research by the identification of a genetic biomarker able to predict men's susceptibility to malignant or benign disease. To the best of our knowledge, this study is the first to analyze 23 DYS loci in PrCa in a Saudi male population and the first to analyze 12 DXS loci in PrCa patients in a Saudi male population, and worldwide. To perform this study, 248 subjects were recruited, comprising 92 patients and 156 healthy controls. All DNA samples were amplified using PowerPlex® Y23 System and Investigator® Argus X-12 QS. The

fragments analysis for alleles of 23 DYS and 12 DXS loci were performed using Genetic Analyzer.

In this study, the results emphasize the influence of genetic elements on PrCa and some alleles of DYS391, DYS437, DYS390, DYS458, DYS481, DYS389II, DYS393 and DYS570 loci in Y-chromosome, as well as some alleles of DXS10135, DXS10146, DXS10148, DXS10079, DXS10103, DXS10101, DXS7132, DXS10134, DXS7423, and HPRTB loci in X-chromosome in Saudi male population. These genetic biomarkers have the potential to be used as a screening method for prediction of susceptibility to PrCa in the Saudi men population, especially those who has high value (> 4 ng/mL) in the PSA test. From the comparisons between Y-chromosome haplotypes comprising different alleles of clusters (1, 2, 3a, and 3b) for 23 DYS loci, it is likely that men who belong to the Y-chromosome lineages with certain haplotypes have a higher risk to develop PrCa or BPH, compared with males having other haplotypes. While, males belonging to lineages with [12, 22, 10, 11] haplotype of cluster 3a are more protected against PrCa either benign or malignant. Furthermore, the comparisons between X-chromosome haplotypes comprising different alleles of clusters (X1, X2, X3, X4), and (lowest GD loci) for 12 DXS loci showed that it is likely that men who belong to the X-chromosome lineages with particular haplotypes have a significantly higher risk to develop PrCa or BPH compared with males having other haplotypes.

The obvious observation in the results of this study that, microvariant alleles (18.2, and 19.2) and (17.2, and 20.2) of DYS458 locus are overrepresented in the PrCa and PBH group in comparison to none in the control group with high OR results; hence, suggesting that men carrying these microvariant alleles of DYS458 locus are at increased risk to develop PrCa or BPH, respectively. Furthermore, microvariant alleles of some X-chromosome loci are overrepresented in BPH group in comparison to none in the healthy control and non in PrCa groups, hence suggesting that men carrying these microvariant alleles are at increased risk to develop BPH. Only one microvariant allele (31.2) of DXS10101 locus is presented more in PrCa group in comparison to BPH group. Therefore, loci that have significant differences in allele frequencies between patients and healthy controls group could be in linkage disequilibrium with tumor-related genes. Although further studies need to be done to confirm this hypothesis.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENGGANTIAN TANDEM PENDEK PADA KROMOSOM X DAN Y BERKAITAN DENGAN RISIKO KANSER PROSES DI PENDUDUK LELAKI SAUDI

Oleh

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Ramalan populasi rentan terhadap sebarang penyakit keturunan adalah salah satu landasan utama genetik manusia. Walaupun terdapat kajian yang berkaitan antara barah prostat (PrCa) dan keturunan alel kromosom keluarga atau frekuensi Y dan kajian lain yang berkaitan antara frekuensi alel kromosom X dan PrCa, kebanyakan mereka tidak dapat disimpulkan kerana bilangan biomarker dan / atau sampel yang terhad serta penyiasatan penanda kromosom seks secara berasingan. Pengulangan tandan pendek forensik (STR) kadang-kadang paling baik untuk mendapatkan maklumat dari penanda keturunan untuk membantu senario warisan tertentu. Oleh itu, banyak kajian dilakukan untuk mewujudkan hubungan antara fenotip dan genotip dalam penyakit itu dengan keturunan Y STR. Penanda keturunan termasuk penanda kromosom Y dan kromosom X dapat membantu analisis kekeluargaan. Oleh itu, kami membuat hipotesis bahawa analisis kedua-dua kromosom X dan Y di samping meningkatkan bilangan penanda yang disiasat menjadi 35 penanda (23 di kromosom Y dan 12 di kromosom X) akan memberikan maklumat hubungan yang komprehensif antara kromosom seks dan PrCa. Sebilangan besar kajian sebelumnya membandingkan pesakit PrCa sahaja dan kawalan yang sihat. Mereka juga memeriksa biomarker genetik pada kromosom Y sahaja. Sementara kajian semasa merangkumi pesakit PCa dan hiperplasia prostat jinak (BPH) serta memeriksa biomarker pada kromosom X dan Y. Beberapa perbandingan dilakukan, tiga di antaranya (pesakit ganas, jinak, dan ganas ditambah jinak), masing-masing, dan kumpulan kawalan yang sihat. Satu lagi perbandingan dibuat antara pesakit jinak dan malignan. Penyelidikan ini dilakukan untuk mengisi jurang dalam penyelidikan dengan mengenal pasti biomarker genetik yang dapat meramalkan kerentanan lelaki terhadap penyakit ganas atau jinak. Sepengetahuan kami, kajian kami adalah yang pertama untuk menganalisis 23 lokus DYS di PrCa pada populasi lelaki Saudi dan yang

pertama menganalisis 12 lokus DXS pada pesakit PrCa pada populasi lelaki Saudi, dan di seluruh dunia.

Untuk melaksanakan kajian ini, kami merekrut 248 subjek yang terdiri daripada 92 pesakit dan 156 kawalan sihat. Semua sampel DNA diperkuat menggunakan Sistem PowerPlex® Y23 dan Investigator® Argus X-12 QS. Analisis pecahan untuk alel 23 DYS dan 12 DXS lokus dilakukan menggunakan Genetic Analyzer.

Dalam kajian ini, hasilnya menekankan pengaruh unsur genetik pada PrCa dan beberapa alel DYS391, DYS437, DYS390, DYS458, DYS481, DYS389II, DYS393 dan DYS570 lokus dalam kromosom Y, serta beberapa alel DXS10135, DXS1014, DXS1014 , DXS10079, DXS10103, DXS10101, DXS7132, DXS10134, DXS7423, dan HPRTB lokus dalam kromosom X pada populasi lelaki Saudi. Biomarker genetik ini berpotensi digunakan sebagai kaedah penyaringan untuk meramalkan kerentanan terhadap PrCa pada populasi lelaki Saudi, terutama mereka yang memiliki nilai tinggi (> 4 ng / mL) dalam ujian PSA. Dari perbandingan antara haplotip kromosom Y yang terdiri daripada alel kluster yang berlainan (1, 2, 3a, dan 3b) untuk 23 lokus DYS, kemungkinan lelaki yang tergolong dalam garis keturunan kromosom Y dengan haplotip tertentu mempunyai risiko yang lebih tinggi untuk mengembangkan PrCa atau BPH, berbanding dengan lelaki yang mempunyai haplotip lain. Sementara, lelaki yang berasal dari keturunan dengan [12, 22, 10, 11] haplotype kluster 3a lebih dilindungi daripada PrCa sama ada jinak atau malignan.

Selanjutnya, perbandingan antara haplotip kromosom X yang terdiri daripada alel kelompok yang berlainan (X1, X2, X3, X4), dan (lokus GD terendah) untuk 12 lokus DXS, menunjukkan bahawa kemungkinan lelaki yang tergolong dalam keturunan kromosom X dengan tertentu haplotip mempunyai risiko yang jauh lebih tinggi untuk mengembangkan PrCa atau BPH berbanding dengan lelaki yang mempunyai haplotip lain.

Pemerhatian yang jelas dalam hasil kajian ini bahawa, alel mikrovarian (18.2, dan 19.2) dan (17.2, dan 20.2) lokus DYS458 terlalu banyak dinyatakan dalam kumpulan PrCa dan PBH berbanding dengan tidak ada dalam kumpulan kawalan dengan hasil ATAU yang tinggi; oleh itu, menunjukkan bahawa lelaki yang membawa alel mikrovarian ini dari lokus DYS458 berisiko meningkat untuk mengembangkan PrCa atau BPH, masing-masing. Selanjutnya, alel mikrovarian dari beberapa lokus kromosom X terlalu banyak dipresentasikan dalam kumpulan BPH dibandingkan dengan yang tidak ada dalam kawalan yang sihat dan yang tidak dalam kelompok PrCa, oleh itu menunjukkan bahawa lelaki yang membawa alel mikrovarian ini berisiko tinggi untuk mengembangkan BPH. Hanya satu alel mikrovarian (31.2) dari lokus DXS10101 yang lebih banyak ditunjukkan dalam kumpulan PrCa berbanding dengan kumpulan BPH. Oleh itu, lokus yang mempunyai perbezaan yang signifikan dalam frekuensi alel antara pesakit dan kumpulan kawalan yang sihat mungkin ada hubungan

ketidakseimbangan dengan gen yang berkaitan dengan tumor. Walaupun kajian lebih lanjut perlu dilakukan untuk mengesahkan hipotesis ini.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AF	African American
AM	Amelogenin
AMOVA	Analysis of Molecular Variance
AR	Androgen Receptor
AS	Asian
ASR	Age-standardized rates
BEN	Benign Prostate Hyperplasia Patients
BBA	Binding Buffer
bp	Base pair
BPH	Benign Prostate Hyperplasia
C	Degree Celsius
CA	Capillary Electrophoresis
ChX	X chromosome
ChY	Y chromosome
CI	Confidence Interval
CLD	Cell Lysis Buffer
CN	Caucasian
CNVs	Copy Number Variations
CON	Healthy Control Subjects
CTCs	Circulating Tumor Cells
CWD	Column Wash Solution
D_c	Discrimination Capacity
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic acid
DRE	Digital Rectal Examination
DXS	DNA X-chromosome Segment
DYS	DNA Y chromosome Segments
FBI	Federal Bureau Investigation
FDA	Food and Drug Administration
FFPE	Formaldehyde-Fixed Paraffin Embedded

FH	Family history
Fst	F statistic
GWAS	Genome Wide Association Studies
GD	Genetic Diversity
H_D	Haplotype Diversity
HGPIN	High-grade prostatic intraepithelial neoplasia
HIFU	High intensity focused ultrasound
HISP	Hispanic
HPC	Hereditary Prostate Cancer
IBD	Identical by Descent
IBS	Identical by State
indels	Insertions and deletions
kb	kilobases
KAMC	King Abdualziz Medical City
KFMC	King Fahd Medical City
LD	Linkage Disequilibrium
L_D	Locus Diversity
LINE	Long Interspersed Elements
LOH	Loss of Heterozygosity
MAL	Malignant Prostate Cancer Patients
µG	Microgram
µL	Microliter
MDS	Multi-Dimensional Scaling
MMR	Mismatch Repair
MSI	Microsatellite Instability
MSTs	Microsatellites
MSY	Male-Specific Region
mtDNA	Mitochondrial DNA
N	Number
NAUSS	Naif Arab University for Security Sciences
NCI	National Cancer Institute
NG	Nanogram

N_H	Number of Haplotype
NRY	Non-recombining Region of the Y-Chromosome
NT	Nucleotide
OL	Off-ladder
OR	Odd Ratio
PARs	Pseudoautosomal Regions
PAT	Prostate Cancer Plus Benign Prostate Hyperplasia Patients
PCA	Principal Component Analysis
PCA3	Prostate cancer antigen 3
PCFH	Prostate Cancer Family History
PCR	Polymerase Chain Reaction
PHI	Prostate Health Index
PI	Paternity Index
PrCa	Prostate Cancer
PSA	Prostate-Specific Antigen
RFU	Relative Fluorescence Unit
SD	Standard Deviation
SINE	Short Interspersed Elements
SNP	Single Nucleotide Polymorphism
SSLP	Simple Sequence Length Polymorphisms
SSR	Simple Sequence Repeats
STR	Short Tandem Repeats
STRAF	STR Analysis for Forensics
UEPs	Unique Event Polymorphisms
USA	United States of America
VNTRs	Variable Number of Tandem Repeats
WGS	Whole-Genome Sequencing
YAP	Y-Alu polymorphism
YHRD	Haplotype Reference Database

CHAPTER 1

INTRODUCTION

The most common cancerous disease among males in the developed countries are the prostate cancer (PrCa) (Goh et al., 2012); moreover, it differs markedly in incidence across ethnic groups. Epidemiological data suggest that PrCa is a multi-factorial disease influenced by both genetic and environmental components; however, the exact reason behind the initiation of this disease was still unclear in most of these patients (Nwosu et al., 2001; Larson et al., 2005; Kim et al., 2007). Therefore, PrCa is one of the malignant diseases which constitute a challenge to the health community due to its high rate among the male population and high mortality rate if it did not discover in early stage (Andersson et al., 2006).

1.1 Background of the study

Prostate Cancer family history (PCFH) is a substantial risk factor for PrCa (Albright et al., 2015; Bruner et al., 2003; Madersbacher et al., 2011). The familial and twin epidemiological studies confirmed the existence of inherited background of this disease; although, the identification of these genetic marker variations was complicated (Goh et al., 2012). This refers to the involvement of many genes in the development of the PrCa disease (Goh et al., 2012). PrCa is the fifth cancer among men in Saudi Arabia with 6.6% incidence rate (Alghamdi et al., 2013; Osman et al., 2014).

Prediction of susceptible population to any hereditary disease is one of the main tracks of human genetics; since, human genetic variations are the differences in DNA sequence within the genome of individuals in populations. Genetic variations in the human genome can take many forms, including single nucleotide changes or substitutions; tandem repeats; insertions and deletions (indels); additions or deletions that change the copies number of a larger segment of DNA sequence; that is, copy number variations (CNVs); other chromosomal rearrangements such as inversions and translocations (also known as copy neutral variations); and copy neutral loss of heterozygosity (LOH) or homozygosity (Ku et al., 2010).

In general, these genetic variations take place naturally in the human genome, and they are the footprints of errors or mistakes that occur in DNA replication during cell division, although external agents, such as viruses and chemical mutagens, can also induce changes in the DNA sequence. The occurrence of each type of genetic variation is mediated by different mechanisms; nonetheless, most of these molecular events or processes are currently unclear and are still

being investigated (Ku et al., 2010). Regardless of the molecular mechanisms or processes that generated the genetic variations, they can be broadly classified as either somatic or germline variations depending on whether they arose from mitosis or meiosis, respectively (Ku et al., 2010).

Since the field of human genetic variations has progressed rapidly over the past few years, it has added much information and deepened knowledge and understanding of the diversity of genetic variations in the human genome. This significant progress has been driven mainly by the developments of microarray and next generation sequencing technologies (Ku et al., 2010).

Although, there were studies related between PrCa and family hereditary (Cannon-Albright et al., 2014) or Y-chromosome alleles frequencies (Carvalho et al., 2010; Cunningham et al., 2007; Ewis et al., 2002; Hameed, Jebor, & Kareem, 2015; Nargesi et al., 2011), and other studies related between X-chromosome alleles frequency and PrCa or benign prostate hyperplasia (BPH) (Alptekin et al., 2012; Biolchi et al., 2012; Cunningham et al., 2007; Gsur et al., 2002b; Neto et al., 2008; Riley & Krieger, 2001), most of it were inconclusive because of the limited number of samples and/or biomarkers as well as the investigation of sex chromosomes' markers separately. Therefore, in the current study it was hypothesized that the analyses of both X and Y-chromosomes together beside increasing the number of investigated markers to 35 markers (23 on Y-chromosome and 12 on X-chromosome) will give a comprehensive linkage information between sex chromosomes and PrCa. To perform this study, 92 patients and 156 healthy control volunteers were recruited. Then, the allelic frequencies of 23 Y and 12 X-chromosomes Short Tandem Repeats (STRs) were calculated. Two new multiplex commercial kits were used for amplification: The PowerPlex® Y23 System (Promega, Cat. # DC2320) (Promega, Madison, USA). and The Investigator® Argus X-12 QS (Qiagen, Hilden, Germany); these markers are known for its allele's variations (highly polymorphic) among populations used for discrimination forensic applications; accordingly, it is expecting to classify the PrCa patients and healthy Saudi males in the control arm according to their allele frequencies; knowing that both category members were living in the same geographical area. Accordingly, categorize population in the future according to their susceptibility or resistance to the disease.

Many studies conducted to establish an association between phenotype and genotype in that disease by STRs lineages (Alptekin et al., 2012; Carvalho et al., 2009; Cunningham et al., 2007; Ewis et al., 2002; Gsur et al., 2002; Hameed et al., 2015; Lindström et al., 2008; Nargesi et al., 2011; Neto et al., 2008; Riley & Krieger, 2001).

Accordingly, there has been considerable research conducted in order to investigate the association between the STRs markers and the incidence of PrCa. This study conducted to find relationship between these markers and the

susceptibility or resistance of Saudi men to PrCa disease and to categorize men according to their genetic profiles, this could help to incorporate genetic variation in the early detection of PrCa (Nam et al., 2009).

Some previous studies present results indicative of no association between some of Y-chromosome markers and PrCa (Kim et al., 2007).

As mentioned above some scientific researches revealed that there are association between genetic back ground and incidence of PrCa and others did not found association; Hence, the scientific research is accumulating work and refinement of previous scientific work, it was decided to check the hypothesis of Ewis et al. 2002, on Saudi population and benefit from the huge progress in the multiplex amplification of X and Y-chromosome to conduct this study on PrCa Saudi patients. Since Saudi population has a higher frequency of Consanguineous marriages (Al Husain and Al Bunyan, 1997; Alharbi et al., 2015; Erzurumluoglu et la., 2016), and there is no study conducted to express this phenomenon; therefore, the Saudi population men with PrCa were adopted to explore these association.

In this study, it was expected to find an association between forensic STRs frequencies on Y-chromosome and the increased risk of developing PrCa; Also, to find a relation between forensic STRs frequencies on X-chromosome and the increased risk of developing PrCa. The main goal was to design a kit that comprised the informative markers to predict the susceptible population in early stages of their life.

1.2 Problem Statement

In the search for novel prognostic genetic biomarkers for PrCa, many tumor markers have been proposed. The number of articles published on this subject has increased substantially in the last decade. However, Prostate-specific Antigen (PSA), Prostate cancer antigen 3 (PCA3) and Circulating Tumor Cells (CTCs) are still the only markers used in clinical practice. Many published results on novel PrCa biomarkers were not reproducible in subsequent studies and thus may never attain the Food and Drug Administration (FDA) approval (Andriole & Wirth, 2011).

The health practitioners in need to an alternative biomarker to the current traditional biomarker to predict the incidence as well as the subsequent clinical symptoms in order to more accurate screening, prevention and therapeutic strategies for prostatic cancer patients due to the diverse genetic background of this disease (Bambury & Gallagher, 2012). The biomarker should improve the predictive accuracy of the multivariate model (Andriole & Wirth, 2011). Though

many new biomarkers are ready for validation, studies need to be carefully designed to test their clinical relevance.

Once the decision to take a biopsy is made, the man becomes a patient, whether he has PrCa or not. This decision presents a difficult challenge, since the man with indolent cancer should not be bothered with a biopsy, yet men with low PSA ranges with aggressive disease must be identified. Thus, there are two main themes in the clinical sphere: 1) develop methods to better predict biopsy outcome, and 2) better predict the prognosis and therapy need/response (Andriole & Wirth, 2011).

Internationally, there are efforts to benefit from the genetics in clinical diagnostic applications to utilizing the genetic variation which related to the disease behaviour. Therefore, the possible role of X and Y-chromosomal haplotypes in PrCa development were explored in a large population-based case-control study of Saudi males. Other benefits from the identification of the male population which susceptible to aggressive symptoms are to recommend for frequent screening and strict prevention strategies besides the early intervention in these population (Goh et al., 2012). The regulation of some modifiable risk which associated with PrCa like lifestyle habits, diet, anthropometric characters and sexual behaviour could be participate in lowering the incidence of the disease (Dagnelie et al., 2004; Wolk, 2005).

1.3 Significance of the Study

The identification of the group or subgroup of males which susceptible more than others to this genetic risk. This approach could decrease the mortality rate in this category of the population. Moreover, decreasing the percentage of men subjected to biopsies or harsh procedure for diagnosis and consequently decreasing the health-related costs.

1.4 Hypothesis

There are an association between certain alleles of 35 forensic lineage STRs on X and Y-chromosomes and the risk of PrCa among Saudi male population.

1.5 Research question

Does the identification of genetic biomarkers on X and Y-chromosome will help to detect the most susceptible individuals to PrCa, increasing the prevention strategies and early intervention and decrease mortality rate?

1.6 General Objective

The purpose of this study is to identify a genetic biomarker on X and Y-chromosome that associated with the risk of PrCa in Saudi male population.

1.7 Specific Objectives

1- To determine the distribution of 12 X-STRs and 23 Y-STRs alleles frequency among Saudi PrCa patients and age-matched healthy Saudi subjects.
2- To identify the X and Y-STR alleles which are more predominant in PrCa patients (susceptible alleles).
3- To identify the X and Y-STR alleles which are more predominant among non-cancer healthy Saudi subjects (protective alleles).
4- To identify the X and Y-STR alleles which are more pre-dominant among BPH patients with elevated PSA levels but negative biopsies.
5- To fill a significant gap in the exhaustive search for PrCa genes throughout the genome.

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LIST OF PUBLICATIONS

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