The Variant Allele Frequency of the IncRNA Prostate Cancer-Associated Noncoding RNA 1 (PRNCR1) rs1456315 C/T Polymorphism in Saudi Population and Colorectal Cancer Risk

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ABSTRACT
Single-nucleotide polymorphisms (SNPs) in long noncoding RNA (IncRNA) genes are associated with the onset and progression of multiple cancers in humans. These SNPs are potential biomarkers for predicting cancer risk. The variable frequency of the IncRNA prostate cancer-associated noncoding RNA 1 (PRNCR1) rs1456315 C/T polymorphism may affect different ethnic groups differently, however, the information lacks for the Saudi population. The aim of this study was to assess the allelic distribution and frequency of the PRNCR1 rs1456315 C/T polymorphism in the Saudi Arabian population, as well as compare it to other populations around the world. PUBMED (Medline) and other related web-databases were referred to extract data from epidemiological studies performed in different ethnic groups. The frequency of PRNCR1 rs1456315 variant allele (C) was found to be 34.62% and a significantly different frequency was observed for the USA (p=0.01), Iran (p<0.007) and China (p=0.01) ethnicity, when the Saudi occurrence is compared to those populations. Present results reveal a distinct pattern of IncRNA prostate cancer-associated noncoding RNA 1 (PRNCR1) rs1456315 polymorphism variant allele in the Saudi Arabian population, which may be due to ethnic differences. The findings could assist in the risk assessment of people harbouring risk allele of rs1456315 SNP and their subsequent cancer susceptibility.

INTRODUCTION
Colorectal cancer results from a combination of epigenetic and genetic changes. The transformation of epithelial cells into colorectal adenocarcinoma could be caused by a variety of biological pathways. Colorectal cancer's genetic basis is represented as a multistep model of cancer onset and progression (Fearon and Vogelstein 1990). Long noncoding RNAs have been identified as important genetic regulators of a vital biological procedure central to risk of developing cancer and many other diseases. RNA transcripts longer than 200 nucleotides that do not code for any proteins are known as IncRNAs (Costa 2010). Some IncRNAs, such as Prostate cancer non-coding RNA 1 (PRNCR1), HOTAIR, and UCA1, are thought to play a role in the progression of cancer.
PRNCR1, a long noncoding RNA downregulated in a variety of cancers, is a 13-kb intron-less lncRNA transcribed from the 8q24 gene (Yang et al., 2016). Previous research has revealed that PRNCR1 is essential for the development of prostate cancer risk, and it may also play a key role in prostate cancer progression by altering androgen receptor (AR) activity.

PRNCR1 has been shown to play a significant role in the development of many cancers in recent studies (Cheng et al., 2018; Pang et al., 2019) along with increased prostate cancer susceptibility by altering the AR system (Yang et al., 2013).

PRNCR1 binds to the acetylated region of the androgen receptor, and its interaction with DOT1L appears to be needed for PCGEM recruitment to the DOT1L-mediated methylation of AR at the N-terminus. These overexpressed lncRNAs' interactions could potentially serve as important regulators in prostate cancer. However, the correlation between the lncRNA PRNCR1 and colorectal cancer development is only recently elucidated. Many studies have suggested that 8q24 variants can play a role in colon cancer susceptibility (Cicek et al., 2009). Despite the fact that PRNCR1 is located in this critical genomic region, its function in Saudi populations for any cancer is yet to be elucidated. The current research compared the frequency distribution of the PRNCR1 rs1456315 polymorphism among normal healthy Saudi Arabians to numerous epidemiologic studies conducted around the world.

**MATERIALS AND METHODS**

**Search Criteria Of Gene Variants:**

PUBMED (Medline), Web of Science, and EGEMS databases were searched for reports that contained the keywords "PRNCR1" "rs1456315" "polymorphism." The searches were restricted to human subjects and written in any language. Studies with genotype frequencies for the control population were included, although studies with only allele frequencies and no genotype frequencies were removed.

The first author's name, the year of publication, the nationality of the subjects, the number of controls, the research type, the inclusion/exclusion criteria, and the frequencies of alleles/ genotypes of the subjects were all abstracted for each of the qualifying studies. When there were several reports from the same race, the data from the most recent publication were used.

The prevalence of the PRNCR1 rs1456315 polymorphism was abstracted from eight studies (AlMutairi et al., 2019; Chung et al., 2011; Li et al., 2016; Li et al., 2013; Li et al., 2021; Salinas et al., 2008; Sattarifard et al., 2017; Xu et al., 2017) and included in the current analysis, which was then compared to the Saudi Arabian population.

**Statistical Analysis:**

Pearson's \( \chi^2 \) test was used to compare genotype and allelic frequencies of different populations using the SPSS statistical software program (version 21). Hardy-Weinberg equilibrium was studied using Court-Lab (a web-based software program). A statistically significant \( p \) value of \( \leq 0.05 \) was used.

**RESULTS**

The minor allele frequency (MAF) of the PRNCR1 rs1456315 polymorphism in the Saudi Arabian population was found to be 34.62 percent according to the genotype distribution, which was in accordance with Hardy–Weinberg equilibrium (HWE) (Table 1). Different minor allele frequencies were found in the genotypic (T/T, T/C, and C/C) and allelic frequency distributions of the studied polymorphism among various populations (Table 2).

When the Saudi Arabian frequency was compared to that of other populations, a substantially different...
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MAF was observed for the ethnicities of the United States (p=0.007), Iran (p=0.01), and China (p=0.01).

**Table 1.** Observed and expected genotypic frequencies of PRNCR1 rs1456315 C/T polymorphism in the control group

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotype observed (n)</th>
<th>Genotype Expected (n)</th>
<th>MAF</th>
<th>p-value (HWE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Mutairi et al., 2019</td>
<td>T/T 61, T/C 48, C/C 21</td>
<td>T/T 56, T/C 59, C/C 16</td>
<td>0.34</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Table 2.** PRNCR1 rs1456315 C/T gene variant genotype and allele frequency distribution in different populations and p-values in contrast to Saudi Arabian population

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/ethnicity</th>
<th>Race</th>
<th>Tumor type in the cases</th>
<th>Genotype</th>
<th>P value</th>
<th>MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Mutairi et al., 2019</td>
<td>Saudi Arabia</td>
<td>Asian</td>
<td>Colorectal Cancer</td>
<td>T/T 61, T/C 48, C/C 21</td>
<td>Ref</td>
<td>34.62</td>
</tr>
<tr>
<td>Salinas et al., 2008</td>
<td>USA</td>
<td>Caucasian</td>
<td>Prostate cancer</td>
<td>T/T 401, T/C 605, C/C 227</td>
<td>0.01*</td>
<td>42.94</td>
</tr>
<tr>
<td>Chung et al., 2011</td>
<td>Japan</td>
<td>Asian</td>
<td>Prostate Cancer</td>
<td>T/T 663, T/C 703, C/C 187</td>
<td>1</td>
<td>34.67</td>
</tr>
<tr>
<td>Li et al., 2013</td>
<td>China</td>
<td>Asian</td>
<td>Colorectal Cancer</td>
<td>T/T 294, T/C 262, C/C 39</td>
<td>0.06</td>
<td>28.57</td>
</tr>
<tr>
<td>Li et al., 2016</td>
<td>China</td>
<td>Asian</td>
<td>Gastric Cancer</td>
<td>T/T 179, T/C 177, C/C 38</td>
<td>0.50</td>
<td>32.11</td>
</tr>
<tr>
<td>Sattarifard et al., 2017</td>
<td>Iran</td>
<td>Asian</td>
<td>Prostate Cancer</td>
<td>T/T 92, T/C 88, C/C 0</td>
<td>0.007*</td>
<td>24.44</td>
</tr>
<tr>
<td>Xu et al., 2017</td>
<td>China</td>
<td>Asian</td>
<td>Breast Cancer</td>
<td>T/T 244, T/C 159, C/C 36</td>
<td>0.01*</td>
<td>26.31</td>
</tr>
<tr>
<td>Li et al., 2021</td>
<td>China</td>
<td>Asian</td>
<td>Lung cancer</td>
<td>T/T 288, T/C 263, C/C 61</td>
<td>0.35</td>
<td>31.45</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Most diseases are multifactorial, resulting from a complex combination of genetic and environmental factors that influence disease progression during life. An increasing body of evidence indicates that genetic variation leads to vulnerability to common diseases like diabetes, cardiovascular disease, and cancer (Eccles and Tapper 2010; Hanahan and Weinberg 2000; Schmith et al., 2003). The discovery of genetic variation linked to common complex diseases is thus a top priority in understanding the pathophysiological mechanisms that underpin common human illnesses. There has been a growing interest in the potential effect of common, functional germline polymorphisms on cancer risk, development and prognosis of cancer.

The genomic variations seen in a group or species are referred to as genetic variation (Nevo 1978), which is also known as a parameter that influences an individual’s phenotype due to the great diversity in the human genome (Kaneko and Furusawa 2006).

Genetic diversity refers to variation in individual genes, and it provides a mechanism for population survival by allowing them to adapt to a constantly changing environment. Genetic variation within and between populations has long been considered to be the secret to understanding the biology of human disease (McKeigue 1997; Shriver 1997; Shriver et al., 2005).

The SNP rs1456315 is linked to a higher risk of CRC, particularly in younger people. Previous research has linked the rs1456315 gene to colorectal cancer, gastric cancer, pancreatic cancer and Prostate cancer (Chu et al., 2017; Li et al., 2016; Li et al., 2013). The SNP rs1456315 has also been found to be significantly associated in Saudi population (AlMutairi et al., 2019) which corroborates an early finding (Chung et al., 2011). Further, PRNCR1 regulates AR activity in the prostate and thus plays an important role in the prostate (Chung et al., 2011). Several other studies have found that AR plays a role in pathological growth. TGFβ is also thought to play a role in the development...
Prostate cancer commonly has a genetic component (Bruner et al., 2003; Lichtenstein et al., 2000; Zeegers et al., 2003). Genetic linkage studies have identified a number of putative loci that may harbor prostate cancer susceptibility genes (Xu et al., 2005), and variant alleles in some candidate genes have been reported to be associated with prostate cancer risk (Rawla, 2019), but the results have proven difficult to replicate (Schaid, 2004).

The 8q24 region's discovery is noteworthy for the effective discovery of multiple markers across different ethnicities (Gudmundsson et al., 2007; Haiman et al., 2007). It's worth noting that the original linkage finding resulted from the investigation of a possible linkage signal (Amundadottir et al., 2006). DG8S737 and rs1447295, the two original markers, have received the most attention, but many other SNPs in the 8q24 region have recently been linked to prostate cancer risk. Fine mapping of the 8q24 region with SNPs from genome-wide association studies (Gudmundsson et al., 2007) and follow-up of an early admixture analysis (McKeigue, 1997) have shown that many regions within 8q24 have variants that can influence the susceptibility of prostate cancer (Witte, 2007).

The global variation of human genomes is the result of a series of evolutionary events such as migration, admixture, population separation, selective pressure, and genetic drift (Balaresque et al., 2007; Barbujani and Colonna, 2010; Henn et al., 2012). Understanding health and disease is supported by genomic imprints conserved in the genomes of diverse populations (Hancock et al., 2011; Scheinfeldt and Tishkoff, 2013). The HapMap project and the Human Genome Diversity Project (HGDP) have recently made important contributions to the evolution of a single nucleotide changes database by documenting genetic differences within individuals of an ethnic group as well as between different ethnicities, globally (Li et al., 2008; Rosenberg et al., 2002; The International HapMap 2005).

An exploration of genetic variation in the Saudi population, which is probably diverse, may contribute to early prevention and intervention strategies. The frequency distribution of the PRNCR1 rs1456315 polymorphic variant in the Saudi population was compared to that of other populations around the world in this analysis. PRNCR1 has been steadily studied as a newly discovered IncRNA that affects tumor cell proliferation, invasion, and apoptosis, and it has become a research target for the early diagnosis and treatment of various cancers. SNPs in PRNCR1, such as rs13252298, rs1016343, and rs1456315, have been linked to the risk of multiple cancers in numerous studies (Chu et al., 2017; Huang et al., 2018; Teerlink et al., 2016).

ncRNAs were found to have a range of biological activities during tumorigenesis and development in several studies. MicroRNAs (miRNAs) and IncRNAs are two subgroups of the ncRNA family that could interact to form a ceRNA network (Chen et al., 2018). LncRNAs have the ability to influence the development of cancer by controlling several biological processes in human cancer through various mechanisms. In Saudi population, the current study reveals a 34 percent frequency of a variant allele (C) of rs1456315, which is substantially different from many other countries such as the United States, Iran, and China. The variant allele frequency of Saudi population was discovered to be higher than Japan, Iran, and China, but lower than the United States. When the Saudi population was compared to the Japanese population and a few cohorts of Chinese
citizens, the frequency distribution of the variant allele was found to be almost identical. rs1456315 is linked with a lower risk of colorectal cancer in the Chinese population, but it has been linked to a substantially higher risk of colorectal cancer in the Saudi population (AlMutairi et al., 2019; Li et al., 2013).

Most SNPs are less penetrant, and diseases polygenic in nature, so differences in allele frequencies among independent datasets can influence the final SNP effect. In genetic-association studies, a shift of 0.02 in MAF will result in significant statistical changes. Furthermore, in the case of two interacting SNPs, a difference in allele frequency of less than 0.1 at the second interacting polymorphism will substantially reduce the independent effect of one SNP (Greene et al., 2009). Racial variation, heterogeneity of the studied population, and variable sample sizes can all contribute to variations in allelic frequency in genetic association studies. Previous studies have shown that the PRNCR1 gene has a wide variety of patterns as compared to various populations around the world (Huang et al., 2018). The different prevalence of these SNPs across populations suggests that susceptibility factors have different effects on different populations.

It's worth noting that the allele and genotype frequencies studied in this analysis don't necessarily reflect the full range of variants at a locus. Such studies, on the other hand, could pave the way for the development of epidemiological and clinical databases in the future. Over the last decade, genome-wide association studies (GWAS) and genetic association studies have resulted in the development of vast data repositories (Pearson and Manolio 2008). Multiple genetic association tests are needed to identify important genes and/or their SNPS involved in the development of early disease prevention programs and treatments. However, several bottlenecks, such as statistical and computational trials, as well as the reproducibility factor, must be addressed before novel genetic biomarkers for use in gene-disease-association research can be identified (Hirschhorn and Daly 2005).

**Conclusion**

The PRNCR1 rs1456315 polymorphism variant allele in the Saudi population varies substantially from that of many other populations around the world. The results may aid in cancer population screening, as well as assessing disease predisposition and significance. Variations in the frequency distribution of the essential Prostate cancer-associated gene in the healthy Saudi population and other racial groups may aid in disease evaluation.

Furthermore, determining the susceptibility factors linked to individual susceptibility and predisposition to diseases such as cancer may reveal details about the etiology of carcinogenesis in the Saudi population. To use this polymorphism as a biomarker for large-scale cancer screening, future large studies investigating gene-gene and gene-environment interactions are needed.

**Conflict of interest**

The author declares no conflict of interest.

**REFERENCES**


Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC,
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