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RESEARCH TITLE

Exploring the genetic dynamics of consanguineous marriages in Libyan populations: A novel focus on the D19S433 short tandem repeats (STRs) marker within Chromosome 19's Centromere Region

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Abstract

This novel study investigates the utilization of a centromeric short tandem repeat (STR) marker to examine the level of homozygosity within the Libyan population. Building upon previous research that highlights challenges in kinship analysis using routine autosomal chromosomal markers. The STRs loci investigation evaluates the efficacy of 15 autosomal STRs markers and how these markers can be used to explore the implications of homozygosity in the context of consanguinity and its potential association with increasing instances of cancer risks.

This study focuses on assessing the level of inbreeding within the Libyan population through the utilization of centromeric short tandem repeats (STRs) markers. The aim is to investigate the frequency of homozygosity, particularly in the D19S433 marker located in the centromere region, among consanguineous groups compared to non-consanguineous groups. The centromere's role in recombination suppression and the potential implications for passing ancestral genes to offspring are explored. The study includes a comprehensive examination of DNA profiling, consanguinity, and its possible associations with cancer risks in the context of the unique genetic and demographic characteristics of the Libyan population.

Key Words: Consanguinity, STRs marker, D19S433, cancer, Libyan population

Introduction

Kinship analysis in forensic genetics has witnessed significant growth in recent decades, driven by the demand for robust markers capable of resolving complex relationships. While routine autosomal chromosome short tandem repeats (STRs) loci have been widely employed, challenges persist in accurately discriminating between close relatives and unrelated individuals. The study underscores the advantages of streamlining kinship cases into pairwise analyses, potentially reducing the number of individuals involved. However, the limitations of existing STRs loci in precisely distinguishing various degrees of relatedness necessitate the exploration of alternative markers (Nothnagel et al., 2010).

The focal point of this research is a set of 13 autosomal STRs markers, including clusters of closely linked markers, designed to overcome the limitations of routine autosomal chromosome STRs loci. A multiplex PCR system was developed to simultaneously analyze these markers, aiming to enhance their applicability in forensic contexts (Albastaki et al., 2022). The primary objective is to evaluate the effectiveness of this set of linked STRs for kinship analysis within the Libyan population (Wyner et al., 2020).

DNA profiling, centromeres loci and oncogenes.

The study provides a comprehensive overview of DNA profiling, emphasizing the significance of short tandem repeats (STRs) loci as markers to distinguish individuals. The Combined DNA Index System (CODIS) loci, a common set of 13 STRs loci in most of commercial kits for human identification, are introduced for instance, as a core component of DNA profiling. Additionally, certain commercial kits, such as the Qiagen kit for human identification, incorporate two additional STRs loci, namely D2S1338 and D19S433, to enhance the profiling process. Centromeres play a critical role in chromosome segregation, ensuring the accurate separation of sister kinetochores during mitosis. Notably, in the Qiagen commercial kit, the D19S433 marker stands out as the sole marker located near the centromere region (chromosome 19 - 19q12), as depicted in Figure 1. The association between centromeres and heterochromatin, the densely packed chromatin surrounding centromeres. This condensed structure plays a crucial role in maintaining cohesion between sister chromatids, mediated by cohesins and possibly catenation of DNA strands. The study emphasizes the importance of crossing over in promoting genetic variation, as it prevents chromosomes from being exclusively maternal or paternal, thereby preserving genetic diversity (Talbert and Henikoff, 2010). Several oncological investigations have identified genes situated in the 19q12 locus that are linked to various cancer types, including breast, gastric, prostate, and pancreatic cancers (Neville et al., 2003, Athanasoglou et al., 2006, Natrajan et al., 2012, Fu et al., 2014).

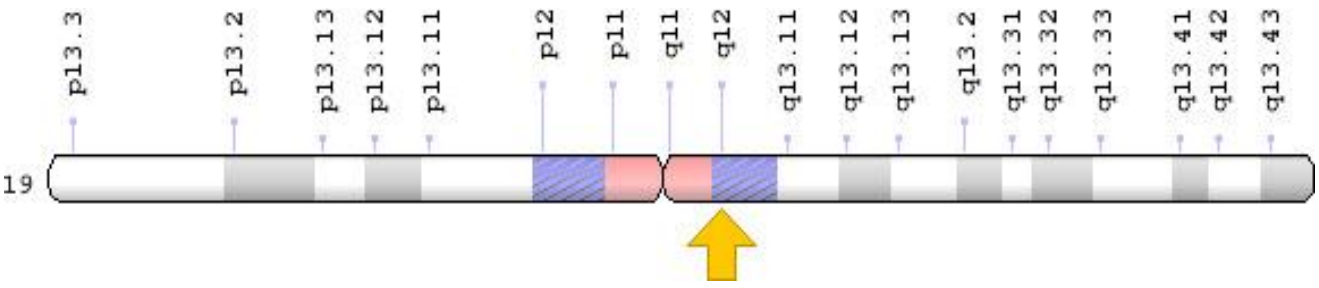

Figure 1. The mapping of the D19S433 marker on chromosome 19 (adapted from (Gholizadeh and Asadi, 2022)).

Consanguinity and Homozygosity

Consanguinity, the practice of marrying close relatives, is a prevalent social norm in many Arab populations, including Libya (Bittles and Hamamy, 2010). This practice contributes to increased homozygosity in offspring, as they are more likely to inherit the identical two alleles from both parents. The study delves into the potential genetic consequences of consanguinity, highlighting its role in the elimination of lethal oncofetal genes from the population gene pool (Abou Jamra et al., 2011).

The study reviews contradictory findings regarding the impact of consanguinity on cancer risks, particularly breast cancer. While some studies suggest a protective effect due to lower frequencies of certain alleles, others associate consanguinity with higher rates of cancer, positing a potential link to recessive cancer-predisposing loci (Bener et al., 2009).

The Libyan Population Overview

A comprehensive overview of the Libyan population is provided, tracing its historical settlements and diverse ethnic composition. The study sheds light on the genetic relationships between the Libyan people and neighbouring regions, revealing closer ties with Tunisian and Egyptian populations. Ethnically, the population is predominantly Arab, with Berbers constituting a minority along with other groups such as Tuareg and Tubo.

The demographic characteristics of the Libyan population, such as population size, growth rates, and family structures, have not been extensively studied in recent years. According to the most recent demographic study available from 2019, it is estimated that the Libyan population was around 5.32 million in 2006 (Daw and El-Bouzedi, 2019). The prevalence of consanguinity and large family sizes, as well as variations in the number of children per family, add layers of complexity to the genetic landscape of the Libyan population (Ibrahim and Serakinci, 2020).

Consanguinity and Cancer Risks

The study explores the potential links between consanguinity and cancer risks, particularly in the context of homozygosity. Contradictory findings from various studies in Arab populations suggest that while consanguinity may increase the chances of homozygosity, its impact on cancer risks is multifactorial and tumour-specific. Some studies propose a protective effect, especially in breast cancer, while others associate consanguinity with an increased risk of certain cancers, emphasizing the need for nuanced research approaches (Bener et al., 2009).

Studies from different Arab countries, including Qatar and Saudi Arabia, present varying perspectives on the relationship between consanguinity and cancer. The presence of null alleles and the high coefficient of consanguinity are factors to be considered when evaluating cancer risks in consanguineous populations. The study also acknowledges the complexity of genetic syndromes associated with specific cancers, emphasizing the need for comprehensive research methodologies (Anwar et al., 2014, Khubrani et al., 2019)

Materials and methods

The study employed a mixed-methods approach to gather data from the Libyan population. A random sample of 71 Libyan individuals residing in the UK was surveyed using a questionnaire to explore the relationships between parents and assess the level of inbreeding within the population. Consent was obtained for buccal swab collection, and DNA analysis was conducted using the QIAamp® DNA Investigator kit. The Investigator IDplex kit, encompassing 13 CODIS core loci plus an additional two STRs markers, D2S1338 and D19S433, was employed to amplify polymorphic STRs markers.

The GeneMapper V3.2 was used to obtain the STRs profiling for all the samples in this study, and all the STRs loci alleles were entered into the Microsoft Excel sheet before conducting the IBM SPSS Statistics V.21 to apply the Chi-square test.

Results

The investigation into homozygosity levels within the consanguineous group yielded noteworthy results, particularly in relation to the D19S433 short tandem repeats (STRs) marker. This specific marker stands out as the sole STRs marker exhibiting a statistically significant outcome within the consanguineous cohort, and it holds a distinctive position within the centromere region (Table 1).

The uniqueness of the D19S433 marker's significance is underscored by its location in the centromere (Figure 1), a region known for exerting recombination suppression effects. This phenomenon suggests that centromere activity plays a crucial role in inhibiting recombination and, consequently, contributes to the transmission of ancestral genes, including potentially mutant ancestral genes, to subsequent generations.

The assessment of homozygosity, specifically measured by the centromeric marker, within the endogamous group substantiates the impact of centromere activity on genetic inheritance. Significantly, the D19S433 marker emerges as the solitary marker displaying a substantial difference (Table 1), with a 48.3% higher frequency of homozygosity in the consanguineous group compared to a mere 7.3% in the non-consanguinity group (Figure 2).

This finding suggests that the centromere, specifically the D19S433 marker, plays a pivotal role in shaping the genetic landscape of consanguineous populations. The observed increase in homozygosity highlights the potential influence of recombination suppression within the centromere region, leading to a higher retention of ancestral genetic material in individuals from consanguineous unions. The specificity of the D19S433 marker's impact emphasizes the importance of considering marker location and centromere activity in understanding the dynamics of genetic inheritance in populations characterized by consanguinity.

Table 1: Chi-square analysis assessing a significant association between homozygosity alleles of all 15 STRs markers and consanguinity.

STRs Markers		Chi-square (P-Value)
1	TP0X	1.000
2	TH01	0.563
3	FGA	0.059
4	D21S11	0.536
5	D19S433*	0.000
6	D18S51	0.637
7	D16S539	0.565
8	D13S317	0.453
9	D8S1179	0.248
10	D7S820	1.000
11	D5S818	0.055
12	D3S1358	0.275
13	D2S1338	0.299
14	CSF	0.434
15	vWA	0.769

* (p-value < 0.05).

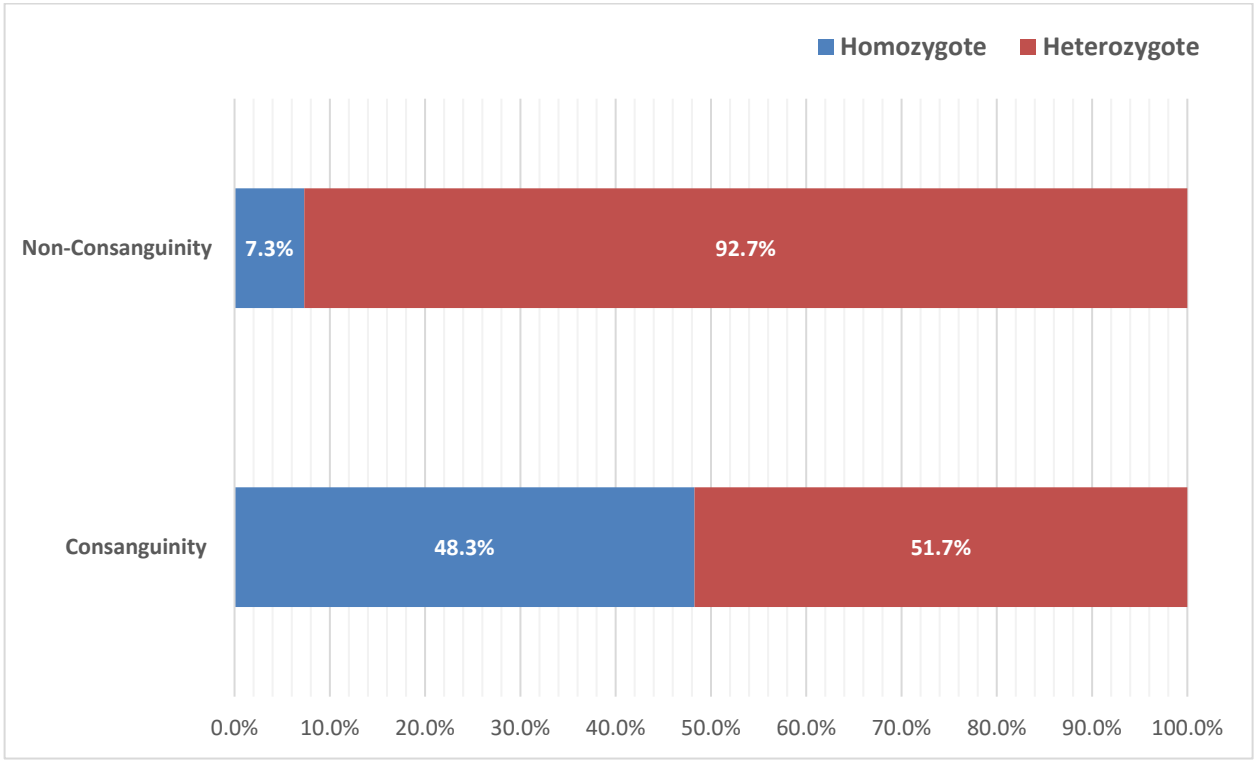

Figure 2: The percentages of homozygosity and heterozygotes alleles in D19S433 STRs marker according to the mating type group (consanguineous and non-consanguineous groups).

Discussion

The results of our study shed light on the intricate relationship between homozygosity, consanguinity, and the unique characteristics of the D19S433 short tandem repeats (STRs) marker located within the centromere. The investigation aimed to unravel the genetic dynamics within consanguineous populations, focusing on the potential impact of centromere activity on recombination and the transmission of ancestral genes.

The standout finding in our study revolves around the D19S433 marker, the only marker demonstrating a significant result within the consanguineous group in Table 1. This marker's exclusive location within the centromere region adds a layer of complexity to its role in genetic inheritance. The centromere's known function in recombination suppression suggests a mechanism through which ancestral genes, including potentially mutant ones, are passed on to subsequent generations without significant changes.

Our results indicate that when measuring homozygosity through the centromeric marker, the D19S433 marker exhibits a substantial difference between the consanguineous and non-consanguinity groups (Sundararajan and Straight, 2022). The consanguineous group shows a remarkable 48.3% higher frequency of homozygosity for the D19S433 marker compared to the non-consanguinity group's modest 7.3%. This stark contrast underscores the impact of consanguinity on the genetic makeup of populations, particularly in regions associated with recombination suppression.

The observed increase in homozygosity within the consanguineous group aligns with expectations based on the known effects of consanguineous unions. The higher retention of ancestral genetic material, as indicated by the D19S433 marker, suggests that consanguinity plays a pivotal role in shaping the genetic diversity of populations (Bittles and Hamamy, 2010). This finding supports previous studies highlighting the link between consanguinity and homozygosity, emphasizing the need to consider specific genetic markers and their locations (Alkuraya, 2010). Furthermore, our results contribute to the broader understanding of centromere activity and its implications for genetic diversity. The centromere's role in suppressing recombination, particularly in the context of consanguineous unions, highlights the intricate mechanisms influencing genetic inheritance and many cancer mechanisms inside the endogamous population (Bener et al., 2009, Mishra et al., 2020). The specificity of the D19S433 marker impact underscores the importance of marker selection in genetic studies, urging researchers to consider the genomic context and functional significance of markers.

In conclusion, our study provides valuable insights into the interplay between consanguinity, homozygosity, and the unique characteristics of the D19S433 marker within the centromere region. The results deepen our understanding of genetic dynamics in consanguineous populations and emphasize the need for further exploration into the role of specific genetic markers and their locations in shaping the genetic landscape.

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