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ORIGINAL RESEARCH

Consanguinity and Occurrence of Monogenic Diseases in a Single Tertiary Centre in Riyadh, Saudi Arabia: A 2 Years Cross-Sectional Study

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Background: Consanguinity, or the practice of marrying close relatives, is a common cultural tradition in Saudi Arabia, with rates among the highest in the world. This practice has significant implications for the prevalence and distribution of major single genetic defects and chromosomal abnormalities within the Saudi population.

Methods: Herein, using the BESTCare electronic medical record system (designed to streamline hospital operations, enhance patient care, and improve the overall efficiency of healthcare services; bestcare.ezcaretech.com) in a single tertiary centre, King Abdullah Specialized Children Hospital (KASCH) in Riyadh, Saudi Arabia, we performed a cross-sectional study for all patients referred to the hospital from the 1st January 2020 until 1st January 2022.

Results: The present study, which included 1100 individuals, found a high prevalence of consanguinity (64%) and a significant proportion of third-degree relatives (69%). The mean age of participants was 12.24 years, and the diagnostic rate using advanced molecular genetics techniques was 45%, with whole exome sequencing (WES) being the most common method (43%). The study also noted a significant delay in diagnosis for more than a year in 16% of cases, with a common neurodevelopmental phenotype (18%).

Conclusion: In conclusion, we revealed the prevalence of consanguineous marriages in the KASCH hospital in Riyadh, Saudi Arabia. We also highlighted the most frequently referred phenotype. These findings are consistent with previous research on the prevalence and impact of consanguinity on rare genetic disorders.

Keywords: consanguinity, genetic disorders, autosomal recessive disorders, Saudi Arabia, prevalence of single gene disorder, chromosomal abnormalities

Introduction

Consanguinity, defined as the practice of marrying close relatives, is a widespread cultural custom in many countries, including Saudi Arabia. Consanguineous partnerships have historically been common in Saudi households due to the kingdom's cultural and social fabric, religious beliefs, and traditions. As a result, consanguinity has emerged as a substantial influence on the Saudi population's genetic landscape, notably in serious single-gene disorders.[1]

The Kingdom of Saudi Arabia has experienced a notable upsurge in investigations concerning the correlation between consanguinity and the occurrence of significant genetic diseases. Research has demonstrated a significant correlation between consanguinity and the prevalence of autosomal recessive disorders, including metabolic disorders, sickle cell

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disease (SCD), and thalassemia. Studies revealed that consanguineous communities in Saudi Arabia have a high incidence of inborn errors of metabolism (IEMs) (1:591, which is the highest incidence for IEMs from the region, highlighting the influence of consanguinity on the transmission of these rare genetic conditions.[2,3]

Additionally, among Saudi Arabia's population, consanguineous marriages have been linked to a higher risk of congenital abnormalities and rare genetic syndromes. Research has indicated a correlation between consanguinity and the incidence of rare Mendelian diseases in Saudi families, including intellectual impairments, skeletal dysplasia, and neurodevelopmental problems. These results highlight the intricate relationship in Saudi Arabia between consanguinity and the inheritance of significant single genetic and chromosomal abnormalities.[1,4]

The high rate of consanguinity in Saudi Arabia has been leveraged to accelerate the identification of recessive Mendelian genes; leading to a high diagnostic yield in consanguineous populations.[5] The prevalence of rare diseases in Saudi Arabia is notably high, primarily due to consanguineous marriages. Despite efforts to reduce disease burden, the high rate of consanguinity persists. Some of the most common Mendelian genetics phenotypes in Saudi Arabia as follow: sickle cell anemia, thalassemia, intellectual disability, congenital glaucoma, Bardet–Biedl syndrome, Meckel–Gruber syndrome, organic acidemias, lysosomal storage disorders, retinal dystrophies, hearing loss, and primary microcephaly.[6]

The current study aimed to determine the consanguinity rate in a tertiary center in Saudi Arabia, between 2020 and 2022 at King Abdullah Specialized Children Hospital (KASCH), Riyadh, Saudi Arabia. The study also highlighted different aspects like the most common type of single gene defects and chromosomal abnormalities, the most common disorder, mutation type and pathogenic nature of different identified variants.

Methods

Study Approval

The study was approved from the Institutional Review Board (IRB) of King Abdullah International Medical Research Centre (KAIMRC) IRB/0715/23. The study used the data in a chart review. Data sheets stored and protected by a computer password, with access only limited to the research team.

The current study complies with the Declaration of Helsinki and informed consent form was provided by the parent or legal guardian of patients under 18 years of age.

Study Settings and Participant

This observational cross-sectional study investigates single gene defect, chromosomal abnormalities, distribution, and consanguinity rate at King Abdullah Specialized Children's Hospital (KASCH) in Riyadh, Saudi Arabia.

All patients from both genders with all ages (birth-80 years) referred to the genetic and precision medicine department from 1st January 2020 to 1st January 2022 were considered for the present study.

BestCare System and Data Collection

All the authors were given access to the BESTCare system. The BESTCare system contains a comprehensive digital medical record of the patient's medical history, beginning with the patient's birth. This record allows prompt access to all relevant information, facilitating data collection at appropriate times. The access provided relevant patient medical records, including group variables: gender, age, and diagnosis, with the relevant essential details of genetic results.

For independent variables, the gender and age of the patient were used. The prevalence of consanguinity and the type of single gene defect will function as the study's results and dependent variables. The process started in other departments, where they had clinical suspicion for a phenotype related to a genetic underlying cause. After accepting the referral in GMP, we determined the consanguinity and its degrees from the family pedigree, which is necessary for the subsequent steps.

Molecular Diagnosis

The next step in the diagnostic process involves determining if the results of the genetic testing are positive or negative. Different molecular tests were performed in the labs depending on the disease type such as single gene screening, FISH,

checking for fragile X syndrome, gene panel, chromosomal analysis, CGH, Whole Exome Sequencing (WES), Whole-genome sequencing (WGS) as described previously.[7–10] In the process of a positive test, variants are classified according to ACMG guidelines and pathogenicity of the identified variants are tested using different online tools such as Mutation taster, Varsome etc. WES/WGS sequencing was performed for the cases that were not solved using fluorescence in situ hybridization (FISH), gene panel, chromosomal analysis and comparative genomic hybridization (CGH). In addition, we calculated the delay in diagnosis by subtracting the age of onset of the condition from the age of confirmed diagnosis.

Statistical Tests

The process of data entry and analysis was conducted with the software program JMP. Categorical data such as the type of single gene defect, chromosomal abnormalities, protein alterations, and clinical presentation were presented as frequencies and percentages. Missing values were excluded from the results and explanatory variables, reducing the sample size but not affecting the regression analysis.

Results

In the present study, patients from both genders referred to Genetic and Precision Medicine Department, KASCH, Riyadh, KSA form 1st January 2020 until 1st January 2022 were included. Total 1100 individuals were included in the study, which were characterized and subjected to molecular diagnosis, which includes 54% males and females (46%) (Figure 1A). Consanguinity was observed in 64% of the cases (Figure 1B), while the degree of consanguinity included 3rd degree 69%, 4th degree 21%, 5th degree 2% and 6th degree (8%) (Figure 1C). Whole exome sequencing (WES) technique was performed as the most frequent mood for molecular diagnosis (43%; 471 patients). While other methods of diagnosis included WGS (33%; 366 patients), CGH (13%; 146 patients), Chromosomal analysis (5%; 58 patients), gene panel (3%; 31 patients), Fragile X (1%; 13 patients), FISH (1%; 471 patients), and single gene sequencing was performed for 1% of the cases (07 patients) (Figure 1D).

In the present study, out of 1100 recruited individuals that were characterized using molecular methods, the diagnosis rate was 45%, and 55% did not reveal any molecular diagnosis (Figure 2A). Out of the 45% diagnosed cases, neuro developmental disorder accounts for 18%, inborn errors of metabolism (9%), chromosome abnormalities (8%), Ophthalmology disorders (7%), Endocrine disorders (6%), Cardiomyopathy (6%), skeletal disorder (6%), non-syndromic hearing loss (5%), Anemia (5%), Genetic skin disorders (5%), Muscular dystrophy (5%), Retinal dystrophy (5%), Mitochondrial disease (5%), Polycystic kidney disease (5%), and Immunodeficiency (5%) (Figure 2B). Moreover, regarding the delay in diagnosis, the first year of the patient recruitment had the most delay 16%, 2nd year delay in diagnosis was 6%, 3rd year (4%), 4th year (2%), 5th year (3%), and more than 5-year delay in diagnosis (15%) (Figure 2C).

Discussion

Consanguinity, the practice of marrying close relatives, who share a common ancestor conceive a child together, and the percentage of genes that two people share depends on how closely they are related.[4–6,11,12] One study has illustrated that the national prevalence is 56% from random selection households around the 13 regions of Saudi Arabia. Furthermore, this study indicates that the first cousin marriage is the highest rate among all other types.[11] In addition, a study conducted 30 years ago investigated the prevalence of consanguineous marriages among 3212 Saudi families. The study found that 58% of the families had a total consanguinity rate, indicating that a significant portion of the population practices consanguinity.[13] Therefore, the high rate of consanguinity in Saudi Arabia is a concerning issue, as it has remained the same over the years. Taking into consideration the effects of genetic defects in the couple's offspring.[14] Our study reported the consanguinity rate of 64% of the cases and the most frequent type of consanguinity was the first cousin which account for 69% and this is comparable to the aforementioned studies results.

Single-gene disorders and chromosomal anomalies are among the most well-understood genetic disorders, particularly those with an autosomal recessive inheritance pattern. Even though the majority of these disorders are rare, they affect millions of people around the world. While autosomal recessive single-gene defects account for the majority of disorders, different mutations within the same gene can cause different phenotypes and degrees of severity.[14,15]

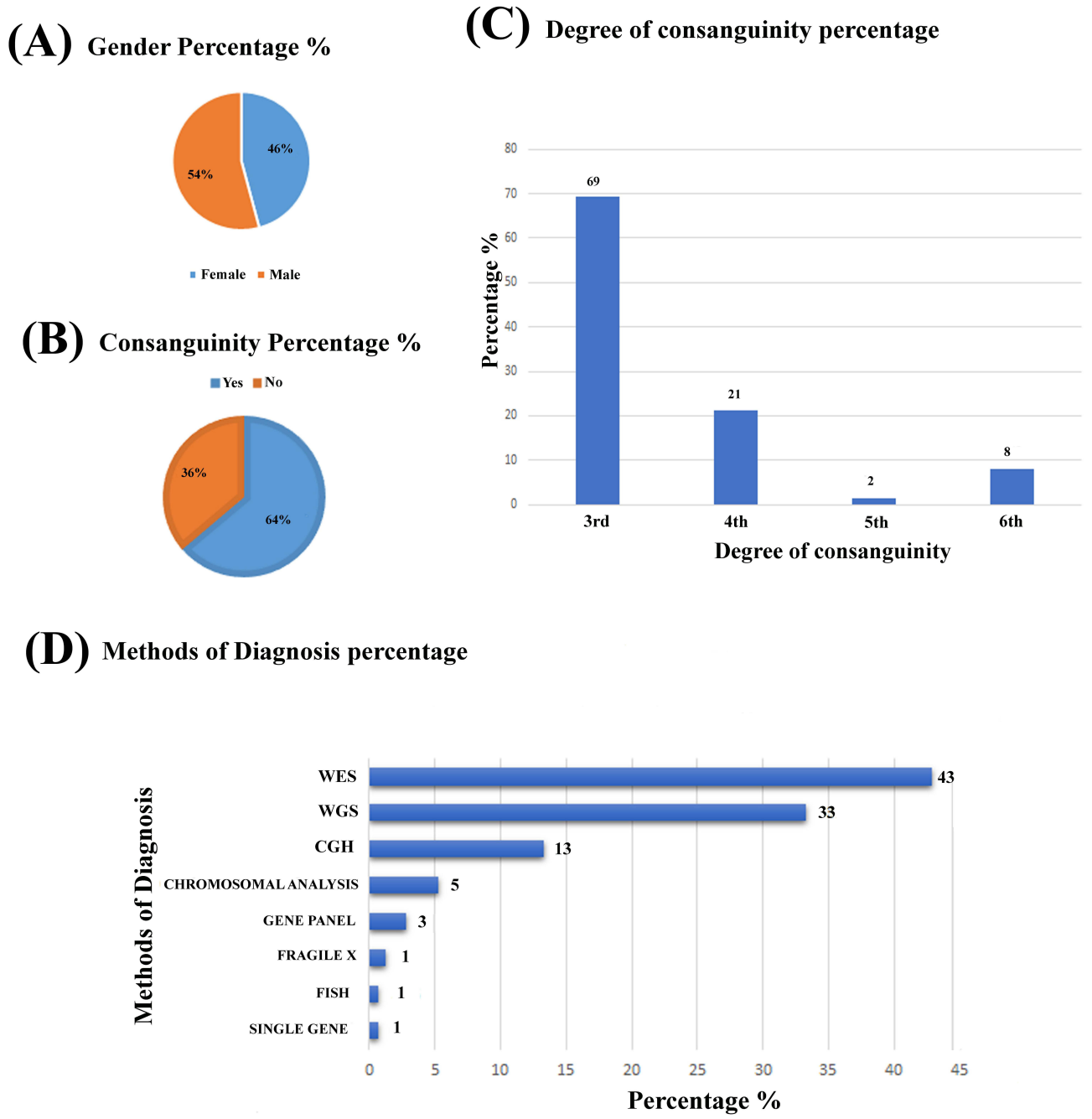

Figure 1 Schematic representation of the patient's data obtained in the present study. (**A**) Percentage of gender observed in the present study: 54% males and 46% females. (**B**) Consanguinity was observed in 64% of the cases. (**C**) Showing the percentage of degree of consanguinity. (**D**) Showing the percentage of Molecular techniques used for molecular diagnosis.

Numerous studies have demonstrated a strong correlation between consanguinity and autosomal recessive diseases.[16,17] Consanguineous marriages had nearly twice the risk of developing autosomal recessive disorders than non-consanguineous marriages. Non-consanguineous marriages exhibited a considerably greater frequency of chromosomal abnormalities than consanguineous marriages.[18,19]

In the present study, 1100 individuals were included (Males: 54% and females: 46%). Whole exome sequencing (WES) technique was performed as the most frequent mood for molecular diagnosis (43%), as WES is frequently used in the clinical practice for molecular diagnosis in all the hospitals in Saudi Arabia compared to the whole genome sequencing which accounts for 33%. Diagnosis rate was observed as 45%. In addition, the first year of patient

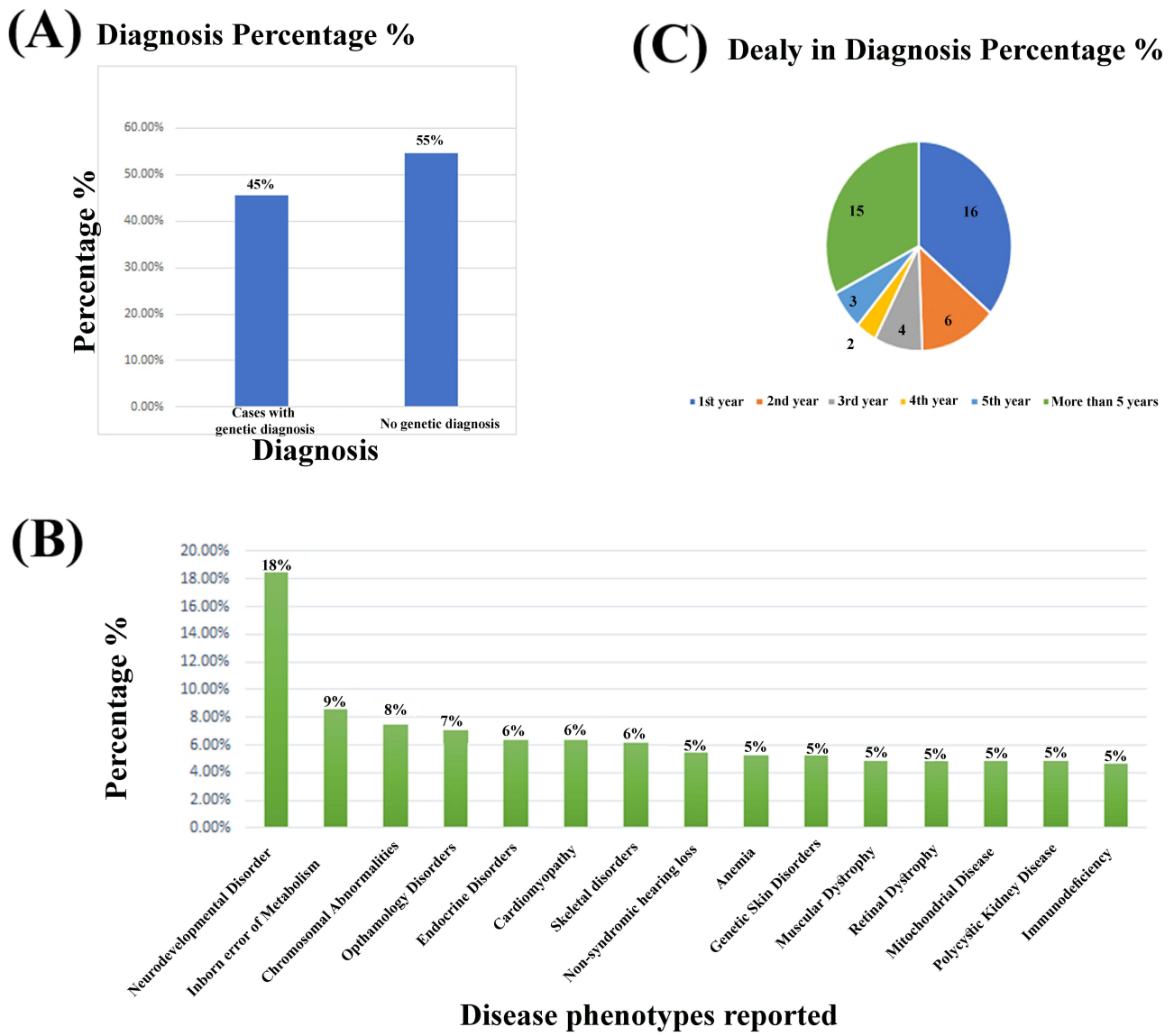

Figure 2 Diagnosis and type of disorders reported in the present study. (**A**) Diagnosis rate observed in the present study: Diagnosed (45%), while 41% did not revealed any molecular diagnosis. (**B**) Percentage of disease phenotypes reported in our cohort. (**C**) Delay in diagnosis observed in the present study.

recruitment experienced the greatest delay in diagnosis 16%. This could be attributed to a delay in the various tests conducted, such as molecular diagnosis and biochemical tests, which require time, as well as the time the main department takes to refer the patient to Genetics and Precision Medicine department. This study is a cross sectional study and small sample size with short duration; therefore, it has its own limitations of selection and information biases in addition to observer biases. Therefore, its result should be taken with caution until further more robust method studies could be conducted and published.

We observed that the type of consanguinity has been associated with different types of disorders. Third-degree consanguinity was associated with a wide range of disorders such as autosomal recessive hearing impairment, Joubert syndrome, primary microcephaly, Kallmann syndrome, Biotin-thiamine-responsive basal ganglia disease (BTBGD), Maturity-onset diabetes of the young (MODY), infantile epileptic encephalopathy, Cardio-facio-cutaneous syndrome, and Alport syndrome. Furthermore, fourth-degree consanguinity was associated with limb–girdle muscular dystrophy, Dias-Logan syndrome, Glucose-6-phosphate dehydrogenase deficiency (G6PD), retinal cone dystrophy, autism–ADHD

and fifth-degree consanguinity was associated with neurodevelopmental disorders. Sixth-degree consanguinity was associated with Cornelia delange syndrome type 1, and glycine encephalopathy (Figure 1C).

This study provides novel insights into the diagnostic landscape of genetic disorders in Saudi Arabia by offering a comprehensive evaluation of whole exome sequencing (WES) versus whole genome sequencing (WGS), revealing WES as the predominant method (43%) in clinical practice. It also highlights a diagnostic rate of 45%, shedding light on the effectiveness of current diagnostic approaches. Notably, the study identifies significant delays in diagnosis during the first year of patient recruitment (16%), attributed to inefficiencies in molecular and biochemical testing and referral processes. By focusing on a tertiary center in Riyadh, the research adds valuable regional data on consanguinity and genetic defects, providing a unique perspective on systemic challenges and practices specific to Saudi Arabia. These findings underscore the need for improved coordination between departments and streamlined diagnostic workflows, offering actionable insights for enhancing genetic counseling and patient management in consanguineous populations.

First cousins are the children of siblings. They share a set of grandparents. First cousins once removed describes the relationship between a person and the child of their first cousin. "Once removed" means there is a difference of one generation. Similarly, second cousins are the children of first cousins. They share a set of great-grandparents. Thus, second cousins once removed suggests that the relationship between a person and the child of their second cousin. "Once removed" indicates a difference of one generation. These notations help understand the degree of genetic sharing among relatives, which is crucial for assessing the risk of genetic disorders, particularly in populations with high rates of consanguinity.[20]

Consanguinity, or marriage between blood relatives, significantly impacts the genetic landscape of populations, particularly in regions where such practices are culturally prevalent. In Saudi Arabia, consanguinity rates are notably high, leading to an increased incidence of major single genetic defects and chromosomal abnormalities. This study, conducted at a single tertiary center in Riyadh over two years, sheds light on the disease burden imposed by consanguinity. The findings not only underscore the importance of genetic counseling and prenatal screening in mitigating these health challenges but also highlight the pivotal role consanguinity plays in gene discovery.[21] By elucidating the genetic underpinnings of rare disorders more prevalent in consanguineous populations, this research advances our understanding of human genetics and disease mechanisms. Moreover, these insights are invaluable beyond Saudi Arabia, as they contribute to global genetic research and inform public health strategies in other countries with high consanguinity rates.[22] Consanguinity rates in different countries where consanguineous marriages are common that include Pakistan (50–70%), Iran (38–48%), Jordan (28–33%), United Arab Emirates (50%), Qatar (54%) and Egypt (20–40%).[23–28] Ultimately, this work underscores the need for continued research and targeted interventions to address the complex health implications of consanguinity.[29,30]

In conclusion, consanguineous marriages are common in Saudi Arabia, and numerous studies have demonstrated that consanguinity can have serious health implications for individuals and families over multiple generations, as well as pose a public health risk. Similarly, if a specific genetic disease is prevalent in a community with high rates of consanguinity, breaking up such consanguineous practices could potentially reduce the incidence of that disease over time. This is because the reduced genetic relatedness between partners would lower the chances of both carrying the same harmful mutations. Thus, the "breakup of consanguinity in such disorders" will help reducing consanguineous relationships in a population can impact the prevalence and frequency of specific genetic disorders. However, due to a lack of extensive research on genetic diseases and disorders, many couples are unaware of the increased risks of their offspring developing genetic illnesses and disorders from birth and throughout childhood. The purpose of our study is to identify the types of genetic disorders and the consanguinity rate in single center in Riyadh, Saudi Arabia. Ultimately, the findings of this study will contribute to a future epidemiological study on genetic disorders in Saudi Arabia.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Ethics Approval

King Abdullah International Medical Research Centre (KAIMRC) IRB/0715/23.

Patient Consent

Obtained from all the members.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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