Vol. 10 No. 2 (2024): 1035-1044
DOI: https://doi.org/10.17720/hom.964

Prevalence, mode of inheritance and some clinical studies of clubfoot disorder among patients

Ayesha Anam[1], Abida Razzaq[2], Muhammad Gulzada[2], Aqeela Nawaz[1], Muhammad Awais Khan[3], Yasir Nawaz[1,*], Fouzia Tanvir[1,*], Muhammad Saleem Khan[1], Shehla Khalid[4], Aqsa Anwar[5], Mutiullah Hameed [6]

1 Department of Zoology, Faculty of Life Sciences, University of Okara, Okara, Pakistan

2 Bahria University Health Sciences Campus Karachi, Pakistan

3 Jinnah Burn & Reconstructive Surgery Centre, Jinnah Hospital Lahore, Pakistan

4 Department of Biotechnology, Abdul Wali Khan University Mardan, Mardan, Pakistan

5 Institute of Molecular Biology and Biotechnology, The University of Lahore, Lahore, Pakistan

6 Department of Zoology, Government College University Lahore, Pakistan

Corresponding author:

Fouzia.tanvir@uo.edu.pk
royyasirnawaz@gmail.com

Abstract

Clubfoot, also known as congenital talipes equinovarus is a group of skeletal disorders characterized by abnormal development and abnormalities in bones, cartilage, joints of legs, ankle and foot. Chondro-osseous growth, morphology, and posture in three dimensions are all impacted by this disorder. One to three cases per one thousand babies are diagnosed with clubfoot, making it most frequent paediatric orthopaedic disease. This study was conducted to assess the frequency, types and patterns of inheritance in villages, schools and hospitals of the Punjab, Pakistan, The study involved surveying 200 families with various genetic disorders in different districts of Punjab. Three families included cousin marriages were selected for further investigation due to their higher prevalence of clubfoot. Among the 139 examined family members, 14 individuals were diagnosed with clubfoot, while the remaining 125 did not show any signs of disorder. The analysis of three families, namely OKR 1, OKR 2, and HRN 3 revealed that the percentage of family members affected by clubfoot was 13%, 9.5%, and 8.63%, respectively. Conversely, the percentage of family members unaffected by clubfoot in these families was 87%, 90.5% and 91.37%, respectively. Further examination of affected individuals showed that out of 14 cases, 13 were males and only one was female. This indicates that males have a higher likelihood of developing clubfoot than females, with male percentage of 92.85% and a female percentage of 7.14%. The observed inheritance pattern of clubfoot disorder among these families was autosomal dominant, autosomal recessive, and X-linked.

Keywords: Clubfoot disease, Skeletal disorder, Inheritance, History, X-linked

Introduction

Skeletal disorders encompass a diverse range of conditions that impact the development and structure of bone, cartilage, and joints (1). Clubfoot encompasses a range of foot deformities, the majority of which are present from birth, known as congenital clubfoot. The condition arises due to abnormally short tendons, which connect muscles to bones. It is a relatively common congenital deformity that typically affects one foot in an otherwise healthy newborn (2). Among these disorders, limb abnormalities are the most common type of congenital deformity. Clubfoot, also

known as congenital talipes equinovarus (CTEV), is a condition that affects the leg, ankle, and foot in three dimensions (3). Many studies have helped us learn more about clubfoot and come up with better ways to treat it. These studies delve into various aspects of the condition, including its aetiology, pathophysiology, and treatment outcomes (4). However, there is less common occurrence known as syndromic clubfoot, which involves the presence of additional congenital abnormalities alongside the foot deformity (5). Although right-foot abnormalities are more common than left-foot ones, it is important to note that about half of infants with clubfoot have the disorder affecting both feet. There are two forms of clubfoot, or congenital talipes equinovarus (CTEV). The majority of cases are classified as idiopathic clubfoot, which refers to isolated clubfoot without any accompanying medical complications (6).

The recognition of clubfoot in ancient Egypt, the early mention of treatment in India, and Hippocrates' contributions all contribute to our evolving knowledge of this orthopaedic condition. These historical perspectives have played a vital role in shaping our understanding and treatment approaches for clubfoot over the centuries (7). This study was designed to record the clubfoot disorder and their clinical investigation in families of different Districts of Punjab.

Material and methods

Site and population

Mix method of study was used in this research in which different observations, some clinical aspects, genetic basis and mode of inheritance were studied. The current study was conducted among some selected families of general population in the duration of one year from March 2021 to March 2023.

The data of 500 patients was collected from different schools, villages and hospitals by visiting during the study period. About 10 schools were selected including Govt. Girls Higher Secondary School Renala, Govt. Girls Model High School Okara, Govt. High School Pattoki,, Government Girls Elementary school 90/12L, Chichawatni, Govt. MC Boys High School, Okara, The Allied School, Renala, Govt. Higher Secondary School Renala, Govt. Girls Model High School Arifwala, Govt. Girls Junior Model High School Haroonabad, Govt. Degree College for Women Lahore around Punjab. About twelve different villages were selected to assess the data including Faridpur, Multan, Faridkot, Khanewal, Gogera, Okara, Chak no 90/12-L, Chichawatni, Chak No. 94/12-L, Ayub park Okara, Govt. colony Okara, Chak No. 97/12-L. A fter this, about five different hospitals were elected i.e., Haji Shareef Hospital 90 Morr, Chichawatni, Rural Health Center RHC 90/12-L, Tehsil Headquarter RENALA, Waseem Surgical Hospital 90 Morr, Chichawatni, RHC 90/12/L, Chichawatni to assess the disease related information and data for study.

Ethical permission and consent to publish

The permission letter from University of Okara, Department of Zoology was obtained to complete the study. The consent form was obtained from affected families of clubfoot disorder to assure that the information and data taken from these families is taken with their complete willingness and harmony without any pressure and could be used for publication.

Questionnaire and data collection

Data was collected through a structured questionnaire. Questionnaire was consisted of two parts. First part of the questionnaire contained demographic question while the other part contained the symptoms of clubfoot disorder.

The survey was conducted in school, colleges, hospital and villages. In this way five hundred Performa were filled by different students of school and colleges. From these Performa's, Performa related to clubfoot disorder were selected. Home of these families were visited and ask about their family from the elder of family.

Pedigree Analysis

Three families were selected for pedigree analysis and all families were detailed interviewed on the spot. The frequency and the mutation of clubfoot disorder in each family were recorded through pedigree analysis. The OKA 1 is the family from one place of Okara. The OKA 2 is the family from seconf place of Okara while the HRN is the place named Haroonabad from Bahawalpur district.

Data Analysis

Clinical symptoms and cousin marriages were analyzed that there are how many first cousin marriages or second cousin marriages. Male and female are analyzed, either male have more chances of clubfoot disorder than female. Rural and urban areas were analyzed. Statistics analysis was performed in MS Excel to check the prevalence and percentage of families of clubfoot disorder.

Results

The objectives of this study were to investigate the prevalence and clinical features of clubfoot disorder among some selected families of different districts of Punjab.

Demographic Characters

The participant characteristics reveal a diverse demographic profile. Of the total participants, 57.55% are male and 42.50% are female. Age distribution shows that 11.50% are 25 years or younger, 25.89% fall between 26 and 35 years, 45.32% are aged 36-45 years, and 17.26% are 45 years or older. Significantly all participants reside in rural areas, with no urban residents included in the study.

Regarding marital status, 37.03% of the participants are in consanguineous marriages, while 62.96% are in non-consanguineous marriages. According to current status, 62.36% of the living participants were male, and 37.63% were female. Among those who have died, 47.82% were male and 52.17% were female. This reveals the rural and predominantly middle-aged nature of the participant group, with a balanced representation of genders and a significant difference in marital practices. This can be seen in table 1.

Table 1: Demographic characteristics of respondents in studied population

Participants Characteristics	**Frequency**	**Percentage %**
Gender		
Male	80	57.55%
Female	59	42.50%
Age		
≤ 25 Years	16	11.50%
26-35 Years	36	25.89%
36-45 Years	63	45.32%
≥ 45 Years	24	17.26%
Residence		

Urban	0	0%
Rural	139	100%
Marital status		
Consanguineous	10	37.03%
Non- Consanguineous	17	62.96%
Alive		
Male	58	62.36%
Female	35	37.63%
Death		
Male	22	47.82%
Female	24	52.17%

Family wise prevalence of disease

This includes study on three families and their association with a condition referred to as clubfoot (CF) disease. Family 1, located at Okara site 1, consists of 39 members, including 4 males and 1 female. Of these members, 5 are associated with CF, representing 13% of the family, while the remaining 34 members are not associated with CF. Family 2, located at Okara site 2, comprises 41 members, including 4 males and no females. In this family, 4 members are associated with CF, which constitutes 10% of the family, while the other 37 members are not associated with CF. Family 3, identified as Haroonabad (HRN), has a total of 58 members, with 5 males and no females. Among them, 5 members are associated with CF, accounting for 9% of the family, leaving 53 members who are not associated with the condition. This is shown in table 2.

Table 2: Family members associated and not associated with clubfoot disease

Family	**Total members**	**Number of Males**	**Number of Females**	**Associated with CF**	**Not Associated with CF**	**Percentage %**
Family 1 (Okara site 1)	39	4	1	5	34	13%
Family 2 (Okara site 2)	41	4	0	4	37	10%
Family 3 (HRN)	58	5	0	5	53	9%

In Family 1, located at Okara site 1, the incidence rate is 13%, with 4 males and 1 female affected. Family 2, situated at Okara site 2, shows an incidence rate of 10%, with 4 males affected and no females. Family 3, identified as HRN, has an incidence rate of 9%, involving 5 males and no females. This is indicated in figure 1.

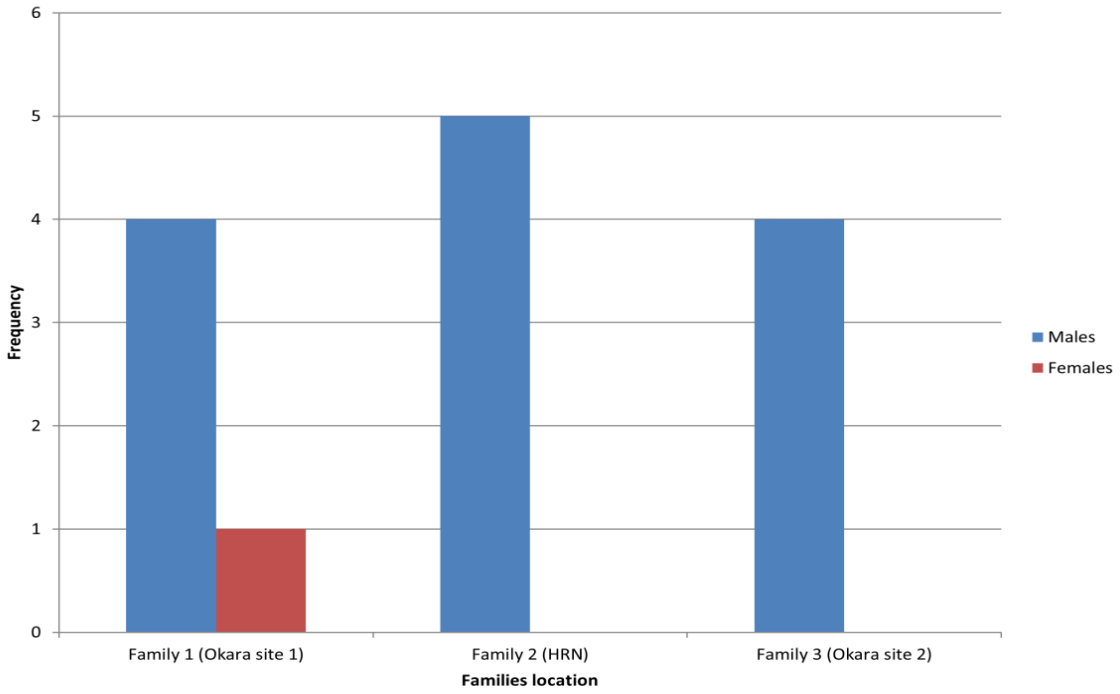

Figure 1: Incidence Rate of Clubfoot in all studied families

Affected families from different sites

The family 1 under study was from District Okara, Punjab, Pakistan, with affected members identified across two generations. Information was gathered through interviews with multiple family members, revealing a history of consanguineous marriages. Physical examinations were conducted on three affected and two unaffected individuals, with blood samples collected from two affected and one unaffected member. A total of five individuals (four males and one female) were found to be affected by this genetic disorder. The pedigree analysis depicted four generations comprising 39 family members, with two affected individuals in the third generation and three in the fourth. This family was affected by clubfoot, as illustrated in Figure 2, with details provided in panels a, b, and c. Clinically, the five affected individuals exhibited similar symptoms, including an inward tilt of one or both feet towards the opposite leg, an abnormally high arch in the foot, depleted calf muscles in one or both legs, abnormal bones and joints in the foot, and an inward and downward turning of the ball of the foot.

Family 2, also from District Okara, Punjab, Pakistan, exhibited affected members across two generations. Information was collected through interviews with various family members, revealing that the parents are related. Physical examinations were conducted on two affected and three unaffected individuals, with blood samples taken from two affected and two unaffected members. In total, four male individuals were identified as being affected by this genetic disorder. The pedigree analysis illustrated four generations consisting of 41 family members, with two affected individuals in the second generation and two in the fourth. Clinically, the four affected individuals exhibited

similar symptoms, including an inward turning of one or both feet towards the opposite leg, a twisted, kidney-shaped foot, and a deep crease on the bottom of the foot, making walking painful and difficult. An abnormally high arch was observed in the foot, with depleted calf muscles in one or both legs, and abnormal bones and joints in the foot. The top of the foot exhibited a downward and inward twist, as shown in Figure 2, with details provided in panels d and e.

Family 3 hails from Haroonabad, Punjab, Pakistan, with affected members identified in two generations. Information was gathered through interviews with various family members, revealing that the parents are related. Physical examinations were conducted on three affected and two unaffected individuals, with blood samples collected from three unaffected and two affected members. In total, five male individuals were identified as being affected by this genetic disorder. The pedigree analysis depicted three generations comprising 58 family members, with one affected individual in the fourth generation and four in the fifth. Clinically, the five affected individuals exhibited similar symptoms, including an inward turning of one or both feet towards the opposite leg, a twisted, kidney-shaped foot, and a deep crease on the bottom of the foot, making walking painful and difficult. An abnormally high arch was observed in the foot, with depleted calf muscles in one or both legs, and abnormal bones and joints in the foot. The top of the foot exhibited a downward and inward twist, with an increase in arch height and inward rotation of the heel. In extreme cases, the foot may appear inverted, and calf muscles are often weak. If only one foot is affected, a slight difference in length, particularly at the heel, may be observed between the two feet. These findings are illustrated in Figure 2, with details provided in panels f, g, and h.

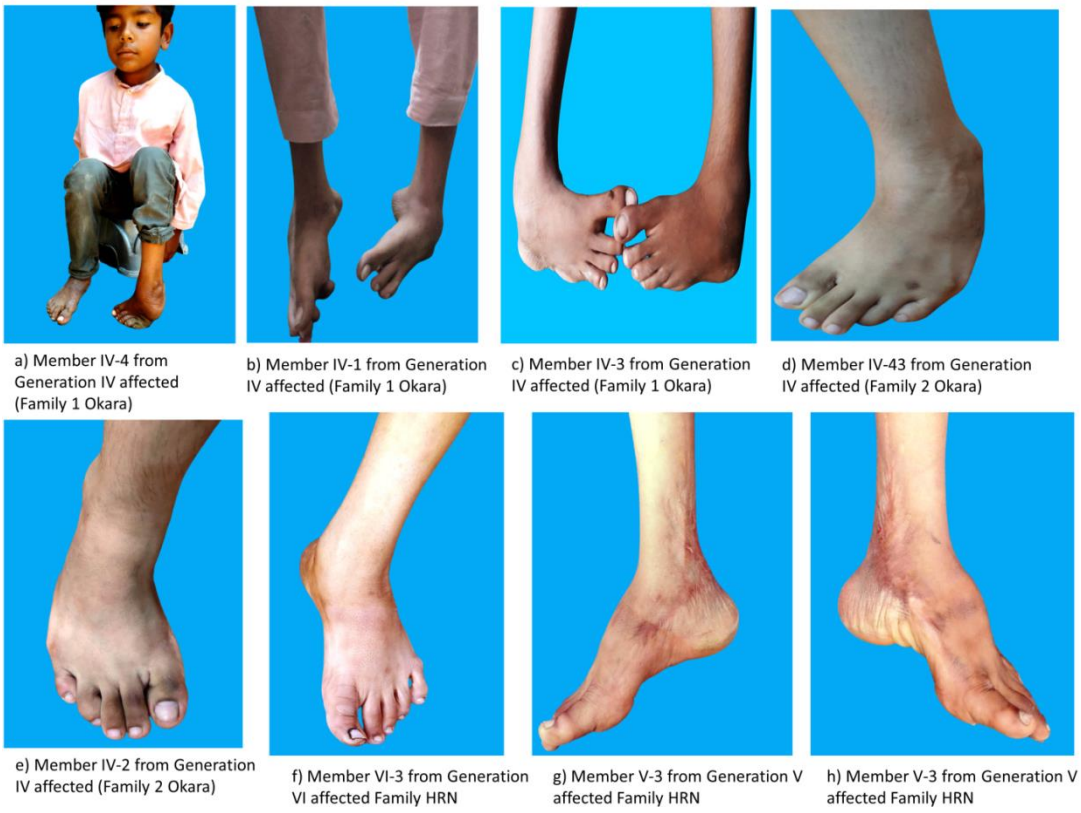

Figure 2: Members from different families affected with disease

Mode of Inheritance among Families

Clinical examination of the affected members, based on available data, indicates that clubfoot disease was present in the fourth generation of Family 1 from Okara. In Family 2 from Okara, the clinical examination suggests that the disorder is an X-linked recessive type of clubfoot. For Family 3 of Haroonabad, the examination reveals that clubfoot is inherited as an autosomal dominant trait. This is shown in figure 3.

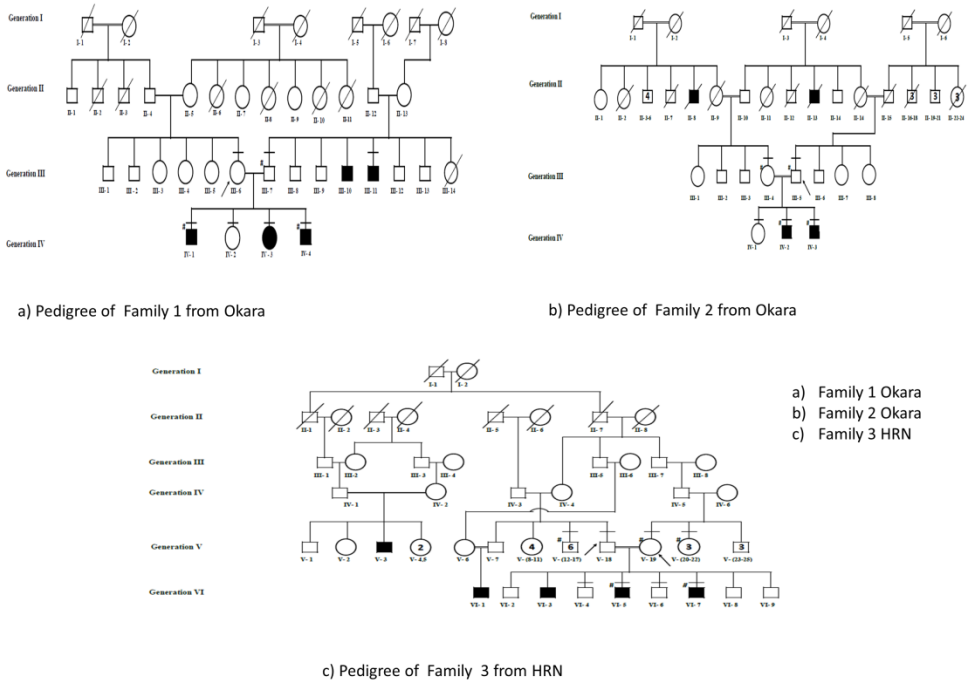

Figure 3: The family history among Club foot disease families

Discussion

The current study was designed to investigate the prevalence of clubfoot disorder with mix research methods for the prevalence rate of clubfoot disorder among some selected families of different districts of Punjab. Clubfoot is characterized by a combination of a severely inwardly twisted foot (equinovarus) and an elevated medial longitudinal arch. These factors, when not addressed, can result in significant challenges and impairments throughout a person's life (8). Congenital talipes equinovarus (CTEV), commonly known as clubfoot, can be classified into two types (9). The majority of cases are classified as idiopathic clubfoot, which refers to isolated clubfoot without any accompanying medical complications. In these cases, the underlying cause of clubfoot remains unknown (10).

The current study showed that the prevalence rate of clubfoot disorder among selected families was 10.07%. The presence behind the prevalence rate of clubfoot disorder among selected families was due to consanguineous marriage. Among 3 families, there were 27 marriages, of which 10 (37.03%) marriages are consanguineous and 17 (62.96%) are non-consanguineous. Marriage inside a family increases the likelihood of contracting an illness when compared to marriage between unrelated individuals (11). Higher postnatal mortality in the children of first-cousin spouses has been linked to the enhanced risk of congenital abnormalities and autosomal recessive diseases that is

associated with consanguineous marriages (12). An estimated one billion people in the present world population are part of societies that give priority to marriage within the same bloodline (13).

Throughout most of the regions of North Africa, the Middle East, and West Asia, consanguineous marriage is a highly respected and revered tradition. Twenty percent or more of all marriages occur inside families in these areas (14). Many studies, including the current one, have shown that there is no correlation between the severity and prevalence of clubfoot disorder and a person's gender. Sixty percent of marriages in Pakistan are between relatives, with eighty percent between first cousins (15). Consanguinity among married couples has also been on the rise, according to new data. There have been records of 54.9% consanguineous marriages, which is equivalent to a mean coefficient of inbreeding of =0.044, and the inbreeding rate is significantly greater (=0.0414) among army families in Pakistan, where the frequency of consanguineous marriage is 77.1% (16). Diseases such as cancer, mental illness, heart disease, digestive trouble, high blood pressure, impaired hearing, diabetes, blood disorders, and bronchial asthma were more common in people with consanguineous parents compared to those with non-consanguineous parents (17). The threat was significantly higher when the parents were first cousins or more closely related. In addition, the evidence at hand indicated that all affected people had a history of clubfoot disorder dating back to childhood. People under the age of 25 made up the entirety of the impacted population. Thirteen males (92.85%) and one female (7.14%) participated in the current investigation.

Clinical investigations showed that they cannot walk easily. It is impossible to walk normally because one or both feet are turned in towards the other leg. The foot is twisted and kidney-shaped. Walking is painful and difficult because of the deep crease on the bottom of the foot. An abnormally high arch can be seen in the foot. One or both legs have a depleted calf muscle. The bones and joints in the foot are abnormal. The ball of the foot curls inward and downward. The findings of our research indicate a clear association between consanguineous marriages and clubfoot disorder in certain families. Consanguinity increases the likelihood of inheriting recessive, dominant and x-linked genetic disorders (18). The higher incidence of clubfoot disorder observed in the families studied suggests a potential genetic basis for this condition. Consanguinity leads to an increased risk of offspring inheriting homozygous recessive alleles, which can result in the expression of deleterious genetic mutations associated with clubfoot disorder (19).

It is important to note that not all individuals from consanguineous marriages will experience clubfoot disorder. The expression of genetic disorders is influenced by various factors, including the specific recessive alleles carried by the parents, the presence of additional genetic modifiers and the complex interplay between genetics and environmental influences. By the pedigree analysis of these families, it is indicated that the mode of inheritance of clubfoot disorder was dominant, recessive and X-linked mode of inheritance pattern.

Conclusion

It is concluded that the effectiveness of clubfoot disorder varies among the different families, with males being more frequently affected than females. The prevalence rate of clubfoot disorder differed across the families, with Family 1 showing a rate of 13%, Family 2 at 8.63%, and Family 3 at 9.5%. Notably, Family 1 had the highest prevalence rate, with 5 out of 39 members affected, primarily observed in the fourth generation. The researchers aimed to identify

the genetic factors contributing to the manifestation of clubfoot. This study seeks to provide a genetic basis for diagnosing clubfoot by locating the chromosomal region harboring the disease-causing gene responsible for the disorder's characteristic phenotype. By exploring whole-genome scans, this research aims to identify novel genes associated with specific diseases, thereby advancing our understanding of the genetic and molecular mechanisms underlying this rare autosomal dominant disorder. The study recommends that the government launch a campaign through hospitals, television, and social media to discourage consanguineous marriages, thereby reducing the incidence of clubfoot disorder.

Acknowledgment
Authors are thankful to the university department for completing the whole work.

Author's contribution
All authors contributed equally in the manuscript.

Funding
None

Conflict of interest
None

References

1.Van Der Heijde D, Daikh DI, Betteridge N, Burmester GR, Hassett AL, Matteson EL, et al. Common language description of the term rheumatic and musculoskeletal diseases (RMDs) for use in communication with the lay public, healthcare providers and other stakeholders endorsed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). 2018;77(6):829-32.

2.Milligan SJ. The Treatment of Infants in Classical and Hellenistic Greece: University of Glasgow (United Kingdom); 1989.

3.Chaudhary R, Samal N, Chaudhary SJJoPRI. Three Dimensional (3D) Assesment of Clubfoot. 2021;33(62A):118 22.

4.Sætersdal C, Fevang JM, Fosse L, Engesæter LBJAo. Good results with the Ponseti method: a multicenter study of 162 clubfeet followed for 2–5 years. 2012;83(3):288-93.

5.Roye BD, Hyman J, Roye Jr DPJPir. Congenital idiopathic talipes equinovarus. 2004;25(4):124-30.

6.Gurnett CA, Boehm S, Connolly A, Reimschisel T, Dobbs MBJDM, Neurology C. Impact of congenital talipes equinovarus etiology on treatment outcomes. 2008;50(7):498-502.

7.Parsa A, Moghadam MH, Jamshidi MHTJAob, surgery j. Relapsing and residual clubfoot deformities after the application of the ponseti method: a contemporary review. 2014;2(1):7.

8.Chandrashekaran G. Clinical Study of soft tissue release for cogenital talipes equinovarus by cincinnati approach: Rajiv Gandhi University of Health Sciences (India); 2010.

9.Gray K, Pacey V, Gibbons P, Little D, Burns JJCdosr. Interventions for congenital talipes equinovarus (clubfoot). 2014(8).

10.Roye Jr DP, Roye BDJJ-JotAAoOS. Idiopathic congenital talipes equinovarus. 2002;10(4):239-48.

11.Hamamy HJJocg. Consanguineous marriages: preconception consultation in primary health care settings. 2012;3:185-92.
12.Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HAJRh. Consanguinity and reproductive health among Arabs. 2009;6(1):1-9.
13.Modell B, Darr A. Genetic counselling and customary consanguineous marriage. Nature Reviews Genetics. 2002;3(3):225-9.
14.Bittles AH, Black ML. Consanguinity, human evolution, and complex diseases. Proceedings of the National Academy of Sciences. 2010;107(suppl_1):1779-86.
15.Ullah MA, Husseni AM, Mahmood SUJIJCMPH. Consanguineous marriages and their detrimental outcomes in Pakistan: an urgent need for appropriate measures. 2017;5(1):1-3.
16.Hashmi M. Frequency of consanguinity and its effect on congenital malformation-a hospital based study. Journal-Pakistan Medical Association. 1997;47:75-7.
17.Albanghali MAJIJoER, Health P. Prevalence of Consanguineous Marriage among Saudi Citizens of Albaha, a Cross-Sectional Study. 2023;20(4):3767.
18.Shawky RM, Elsayed SM, Zaki ME, El-Din SMN, Kamal FMJEJoMHG. Consanguinity and its relevance to clinical genetics. 2013;14(2).
19.Wierenga KJ, Jiang Z, Yang AC, Mulvihill JJ, Tsinoremas NFJGiM. A clinical evaluation tool for SNP arrays, especially for autosomal recessive conditions in offspring of consanguineous parents. 2013;15(5):354-60.