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CLINICAL AND GENETIC ASPECTS OF MUSCULAR DYSTROPHY IN DIVISION SAHIWAL, PUNJAB PAKISTAN

Original Article

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ABSTRACT

Background: Muscular dystrophy (MD) comprises a group of inherited neuromuscular disorders characterized by progressive muscle weakness, atrophy, and loss of function. These disorders exhibit various inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked transmission. The prevalence and genetic distribution of MD vary across populations, necessitating region-specific epidemiological studies. Understanding the clinical presentation and inheritance patterns of MD is crucial for improving diagnostic strategies and management. This study aimed to investigate the prevalence, inheritance patterns, and clinical characteristics of MD among selected families in Division Sahiwal, Punjab, Pakistan.

Objective: To determine the prevalence, inheritance modes, and clinical manifestations of muscular dystrophy in affected families of Division Sahiwal, Punjab, Pakistan.

Methods: A mixed-method epidemiological and clinical study was conducted, incorporating qualitative and quantitative approaches. A survey was performed across schools, colleges, hospitals, and villages in Division Sahiwal to identify individuals with MD. Families with confirmed cases were selected for detailed pedigree analysis. Seven families, comprising 280 individuals, were examined, and inheritance patterns were assessed. Blood samples were collected from affected individuals for genetic analysis. Data were statistically analyzed using Minitab version 19.0, with frequency and prevalence rates calculated as percentages.

Results: The overall prevalence of MD in the studied families was 10.25%. Among the 280 individuals surveyed, 28 were affected, including 13 males (9.70% of total males) and 15 females (10.27% of total females). Consanguinity was present in 85.71% of families. The highest prevalence was observed in Swl-Vil-MD-89R (13.0%), followed by Swl-Vil-MD-35L (12.1%), Swl-Vil-MD-88R (11.76%), Swl-Vil-MD-99L (11.11%), Swl-Vil-MD-68R (8.1%), Swl-CIT-MD-PC (7.1%), and Swl-Vil-MD-96L (6.25%). Pedigree analysis confirmed the persistence of MD across generations, predominantly following an autosomal dominant pattern.

Conclusion: This study highlights a high prevalence of MD in consanguineous families, emphasizing the need for genetic counseling and public awareness campaigns. Future research should incorporate advanced genetic sequencing to identify specific mutations and develop targeted interventions for disease management.

Keywords: Autosomal Dominant Inheritance, Epidemiology, Genetic Disorders, Muscular Dystrophy, Neuromuscular Diseases, Pakistan, Prevalence.

INTRODUCTION

Muscular dystrophy encompasses a group of inherited disorders characterized by progressive muscle weakness and degeneration due to mutations affecting proteins essential for muscle function. These conditions, which vary in onset, inheritance patterns, and severity, significantly impact patients' mobility and quality of life. The underlying genetic mutations primarily disrupt the glycoproteins in the muscle cell membrane, leading to structural instability and impaired muscle regeneration (1). Among the various forms, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are among the most extensively studied due to their severe progression and X-linked inheritance. DMD, caused by mutations in the dystrophin gene located on Xp21, results in a near-total absence of dystrophin, leading to rapid muscle degeneration and early loss of ambulation (2). In contrast, BMD stems from dystrophin mutations that allow for some residual protein function, yielding a milder but still debilitating phenotype (3). Muscular dystrophy exhibits diverse genetic inheritance modes, including X-linked, autosomal dominant, and autosomal recessive patterns (4). For instance, Emery-Dreifuss muscular dystrophy (EDMD) may follow X-linked, autosomal dominant, or recessive inheritance due to mutations affecting emerin or lamin A/C proteins (5). Similarly, limb-girdle muscular dystrophy (LGMD) can be either autosomal dominant or recessive, with the latter form typically presenting earlier and progressing more rapidly (6). Facioscapulohumeral muscular dystrophy (FSHD), an autosomal dominant disorder, is associated with a 3.3 kb deletion on chromosome 4, leading to abnormal expression of the DUX4 gene, which contributes to progressive muscle atrophy (7). Myotonic muscular dystrophy (DM), the most common adult-onset form, is linked to expanded CTG trinucleotide repeats in the DMPK gene, affecting various physiological functions beyond muscle tissue (8).

The etiology of muscular dystrophy is closely tied to disruptions in glycoproteins within the muscle membrane, which compromise cellular integrity and function. The dystrophin gene, the largest known human gene spanning 79 exons, is highly susceptible to spontaneous mutations, accounting for its high mutation rate (9). This genetic complexity contributes to both allelic and nonallelic heterogeneity, where different mutations in the same gene or different genes produce overlapping phenotypic manifestations, complicating genetic diagnosis and therapeutic interventions (10). Understanding the intricate genetic basis of muscular dystrophy is crucial for advancing targeted treatments, including gene therapy, exon-skipping strategies, and pharmacological interventions aimed at restoring dystrophin function or modulating disease progression (11). Despite significant advancements in genetic research, muscular dystrophy remains a largely incurable disorder, with management focusing on symptomatic relief, supportive care, and emerging experimental treatments (12). The complexity of inheritance patterns and the diverse phenotypic spectrum underscore the need for precise molecular diagnosis and tailored therapeutic approaches. Given the genetic and clinical variability of muscular dystrophy, further research is essential to elucidate genotype-phenotype correlations, refine diagnostic tools, and develop more effective interventions. This study aims to explore the clinical and genetic landscape of muscular dystrophy in the Division of Sahiwal, Punjab, Pakistan, to contribute valuable insights into its epidemiology, inheritance patterns, and potential therapeutic implications.

METHODS

The study employed a mixed-method research design, integrating both epidemiological and clinical approaches to comprehensively investigate the clinical and genetic aspects of muscular dystrophy in Division Sahiwal, Punjab, Pakistan. Both qualitative and quantitative data were collected and analyzed within a single study framework to provide a holistic understanding of the disorder. The study population comprised individuals with suspected or confirmed muscular dystrophy across various age groups. Families exhibiting symptoms of muscular dystrophy were identified through an extensive survey conducted in public and private schools, colleges, hospitals, and villages in both urban and rural areas. Inclusion criteria encompassed individuals with clinical signs of muscle degeneration, confirmed cases of muscular dystrophy, and family members of affected individuals willing to participate in pedigree analysis. Exclusion criteria included individuals with other neuromuscular disorders not classified under muscular dystrophy and those unwilling to provide informed consent (13). To collect data, a structured survey was conducted across educational institutions and healthcare facilities. A list of government and private schools, colleges, and hospitals in Sahiwal was systematically surveyed to identify affected individuals and families. Field visits to villages were conducted to ensure representation of both urban and rural populations. Meetings with families were arranged to document clinical manifestations and inheritance patterns. Seven families with a confirmed history of muscular dystrophy were selected for detailed pedigree analysis. Each family provided informed consent for participation, including permission for photographic documentation of affected individuals. Blood samples were collected for genetic analysis, including DNA extraction and gene sequencing, to determine the specific mutations associated with the disorder (14-16).

The study area encompassed Division Sahiwal, with permissions obtained from relevant authorities. Ethical approval was secured from the Institutional Review Board (IRB) of the Department of Zoology, University of Okara. Additionally, authorization letters from the

Deputy Commissioner of Sahiwal facilitated access to schools, colleges, and healthcare facilities for data collection. Written consent was obtained from all participants, ensuring voluntary participation and adherence to ethical research practices (17-19). Pedigree analysis was conducted for the seven selected families to determine the inheritance patterns and assess the prevalence of the disorder within familial lineages. The data collected from pedigree studies were used to trace mutation patterns and inheritance trends. Statistical analysis was performed using Minitab software version 19.0. Frequency and prevalence of muscular dystrophy cases were calculated, and results were expressed as percentages to provide epidemiological insights (20-23). All ethical considerations were strictly adhered to throughout the research process. Participants provided written informed consent before data collection, ensuring that participation was voluntary and confidential. Ethical approval was granted before initiating the study, and all procedures complied with research ethics guidelines, protecting the rights and privacy of the participants (24,25).

RESULTS

The study investigated the prevalence and clinical characteristics of muscular dystrophy in selected families of Division Sahiwal. A total of seven families were examined, consisting of 280 individuals, including 134 males (47.85%) and 146 females (52.14%). Among the participants, 164 individuals were alive, while 116 had deceased. The prevalence of muscular dystrophy among the studied families was 10.25%, with 28 individuals identified as affected. The prevalence was determined by calculating the number of affected individuals relative to the total family members. The affected population included 13 males (9.70% of total males) and 15 females (10.27% of total females), indicating a slightly higher prevalence among females. Age distribution analysis revealed that 54 individuals (19.28%) were aged between 7 and 25 years, 98 individuals (35.00%) were in the 26–35-year range, 81 individuals (28.92%) were between 36 and 45 years old, and 47 individuals (16.78%) were above 45 years. The majority of participants resided in rural areas, with 238 individuals (85%) from rural communities and only 42 individuals (15%) from urban settings. Consanguinity was identified as a major contributing factor, with six out of seven families (85.71%) reporting consanguineous marriages, whereas only one family (14.28%) had non-consanguineous marriages. Among the deceased, 52 males (38.80%) and 64 females (43.83%) were recorded.

The distribution of affected individuals varied across the studied families. The highest prevalence was observed in family Swl-Vil-MD-89R, where 3 out of 23 individuals (13.0%) were affected, followed by family Swl-Vil-MD-35L with 9 out of 74 individuals (12.1%) affected. Family Swl-Vil-MD-99L reported 3 affected individuals out of 27 (11.11%), while family Swl-Vil-MD-88R exhibited a prevalence rate of 11.76% (2 out of 17 individuals). In contrast, family Swl-Vil-MD-96L showed a lower prevalence, with 3 affected members out of 48 (6.25%). Family Swl-Vil-MD-68R had 4 affected individuals out of 49 (8.1%), and family Swl-CIT-MD-PC recorded 4 affected members among 42 individuals (7.1%). Pedigree analysis demonstrated that muscular dystrophy was transmitted across multiple generations. The inheritance patterns suggested an autosomal dominant mode in several families, particularly those with limb-girdle muscular dystrophy (LGMD). Family Swl-Vil-MD-35L, which had 9 affected individuals from the 5th and 6th generations, exhibited progressive muscular weakness, primarily affecting the shoulder and pelvic girdle muscles. Clinical evaluation indicated that affected members developed early symptoms between the ages of 5 and 7, with progressive difficulty in walking, standing up from a seated position, and jumping. By the ages of 16–17 years, respiratory complications emerged, and some affected members became immobilized. One individual died at the age of 16 due to respiratory failure.

In family Swl-Vil-MD-96L, 3 affected members, including 1 female and 2 males, exhibited muscle weakness in the shoulder and pelvic regions. Symptoms appeared between the ages of 5 and 7, with increased severity in the female affected member. Family Swl-Vil-MD-68R had 4 affected individuals, all females, with similar progressive symptoms. Family Swl-CIT-MD-PC, comprising 42 individuals, had 3 affected members (1 female and 2 males), all experiencing muscle weakness predominantly affecting the quadriceps femoris and biceps brachii muscles. Symptoms manifested between the ages of 5 and 7 years, with progressive loss of mobility. Family Swl-Vil-MD-88R presented with 2 affected females, while family Swl-Vil-MD-89R and Swl-Vil-MD-99L each had 3 affected individuals, showing symptoms of progressive limb weakness, difficulty in rising from a sitting position, and eventual immobilization. The disease in these families progressed through successive generations, highlighting the hereditary nature of the condition. A strong correlation between consanguinity and disease prevalence was observed, with consanguineous marriages being a significant contributing factor in six out of the seven studied families. This pattern suggests that autosomal recessive inheritance may also play a role in some cases. Blood samples were collected from affected and normal members for genetic analysis, and clinical assessments were performed to document disease progression. Statistical analysis confirmed that the prevalence of muscular dystrophy was higher in families with a history of consanguinity, reinforcing the genetic basis of the disorder.

Table 1: Demographic characters of studied families

Participants characteristics	Frequency	Percentage%
Gender		
Male	134	47.85%
Female	146	52.14%
Age		
7-25 years	54	19.28%
26-35 years	98	35.00%
36-45 years	81	28.92%
45 years	47	16.78%
Residence/ Locality		
Urban	42	15%
Rural	238	85%
Marriage		
Consanguineous families	6	85.71%
Non-Consanguineous families	1	14.28%
Alive		
Male	82	61.19%
Female	82	56.16%
Death		
Male	52	38.80%
Female	64	43.83%

Table 2: Prevalence of muscular dystrophy in different studied families

Sr.#	Family	Affected persons	Total persons	Percentage%
1	Swl-Vil-MD-35L	9	74	12.1%
2	Swl-Vil-MD-96L	3	48	6.25%
3	Swl-Vil-MD-68R	4	49	8.1%
4	Swl-CIT-MD-PC	4	42	7.1%
5	Swl-Vil-MD-88R	2	17	11.76%
6	Swl-Vil-MD-89R	3	23	13.0%
7	Swl-Vil-MD-99L	3	27	11.11%
Total		28	280	10.25%

Table 3: Gender based prevalence rate of Muscular dystrophy

Total no. of families	**07**
Total affected members	28
Total no. of males	134
Total no. of females	146
Total members	280
Total male affected	13
Total female affected	15
The ratio of affected males (out of total males)	9.70
The ratio of affected females (out of total females)	10.27
The ratio of total affected persons	10.25

Table 4: Consanguinity and Non consanguinity

Sr. No.	**Families**	**Consanguinity**
1	Swl-Vil-MD-35L	YES
2	Swl-Vil-MD-96L	YES
3	Swl-Vil-MD-68R	YES
4	Swl-CIT-MD-PC	YES
5	Swl-Vil-MD-88R	NO
6	Swl-Vil-MD-89R	YES
7	Swl-Vil-MD-99L	YES

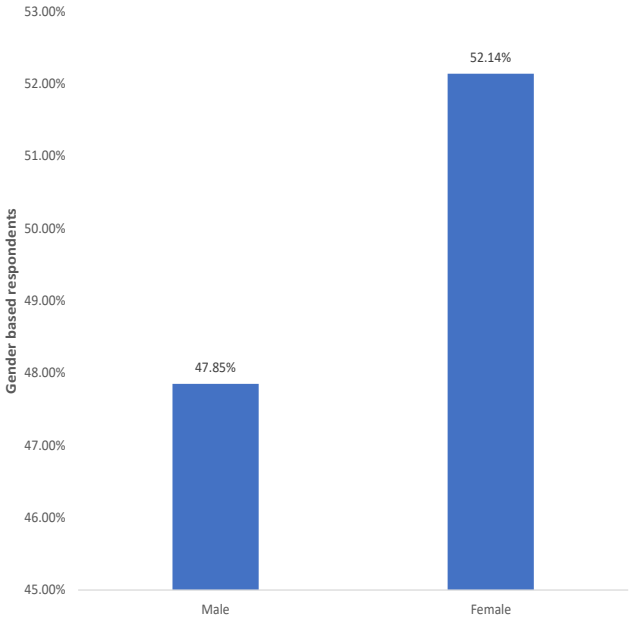


Figure 1 Gender-based respondents

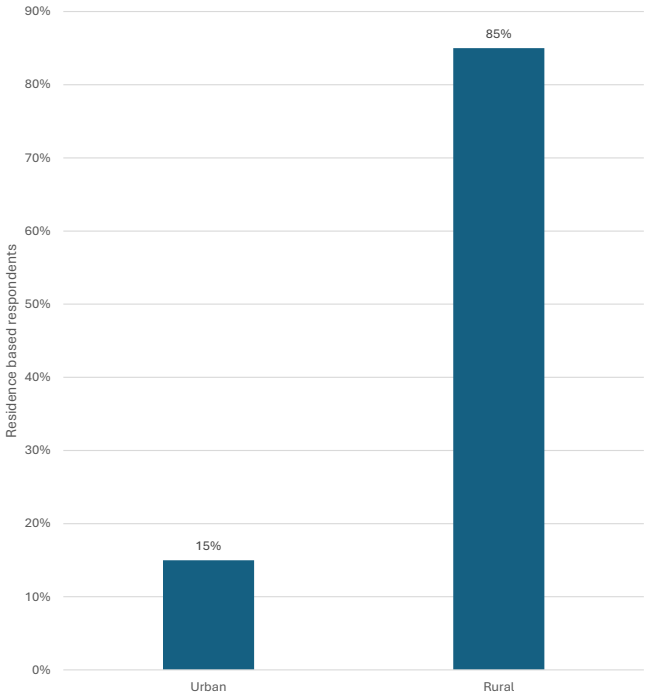


Figure 1 Residence-based respondents

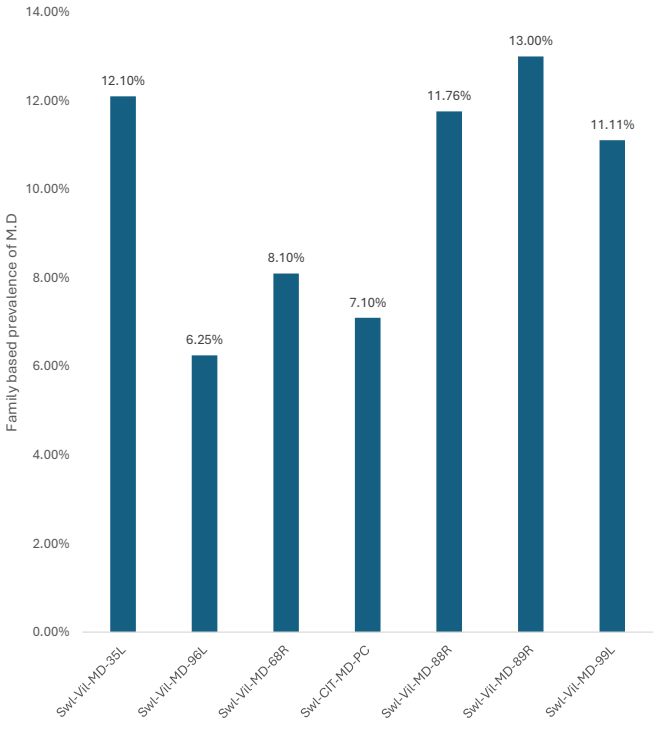
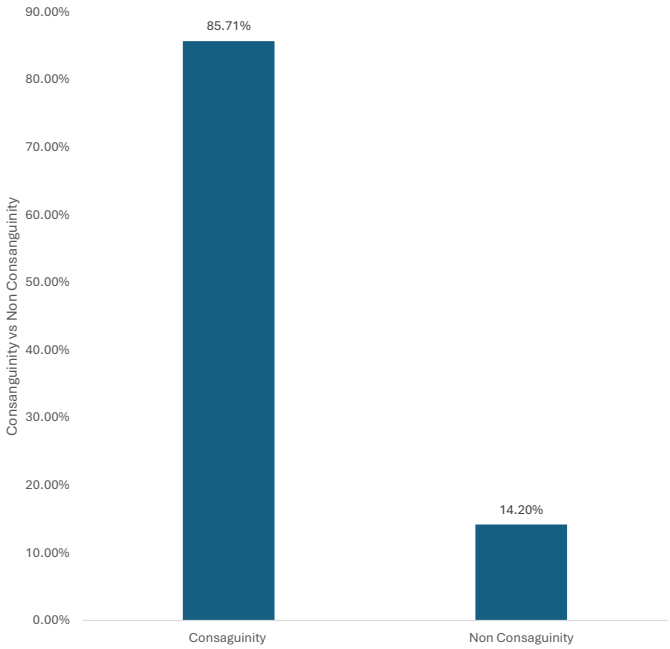


Figure 1Prevalence rate of Muscular dystrophy



. Description of family SWL -VIL- MD-35-L

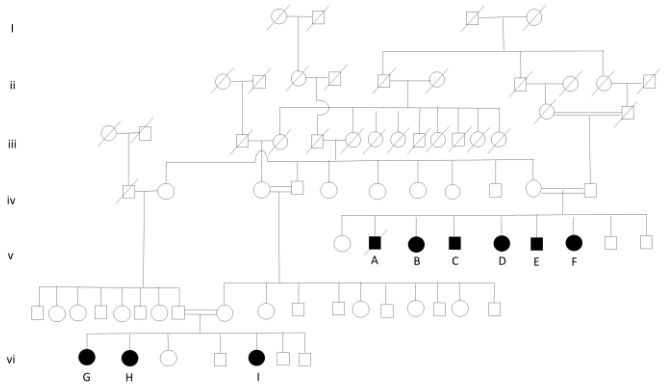


Figure 1:Pedigree SWL -VIL- MD-35-L

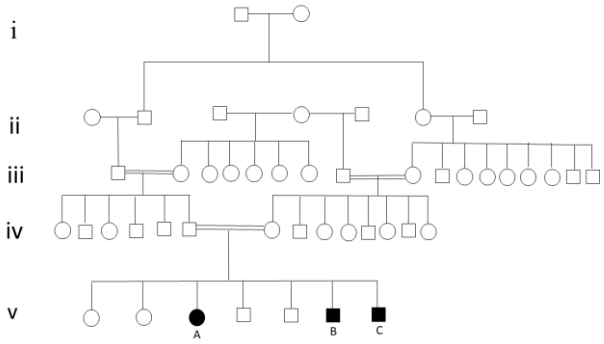


Figure 1:Pedigree SWL -VIL- MD-96-L

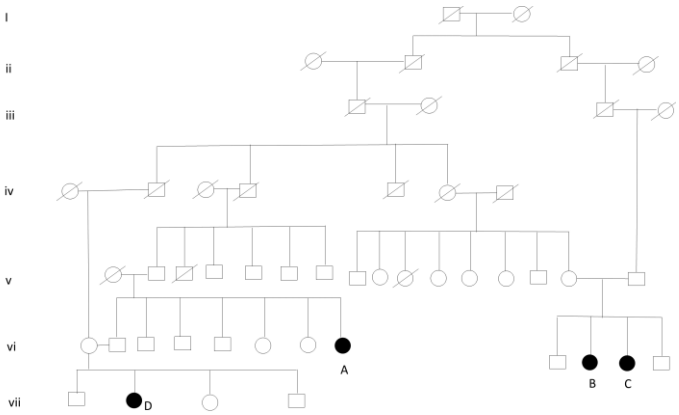


Figure 1:Pedigree SWL -VIL- MD-68-R

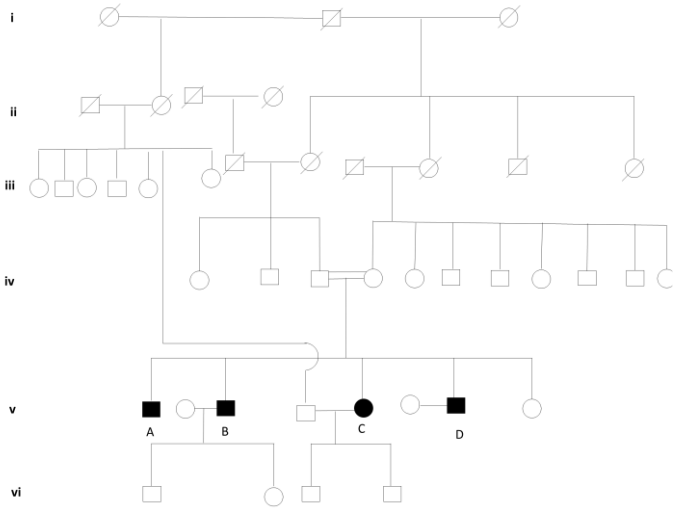


Figure 1:Pedigree Swl-CIT-MD-PC

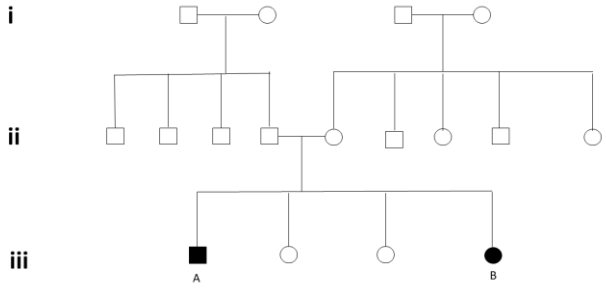


Figure 1:Pedigree Swl-Vil-MD-88R

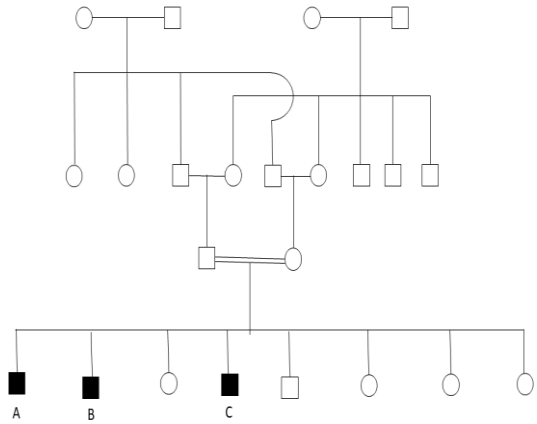


Figure 1:Pedigree Swl-Vil-MD-89R

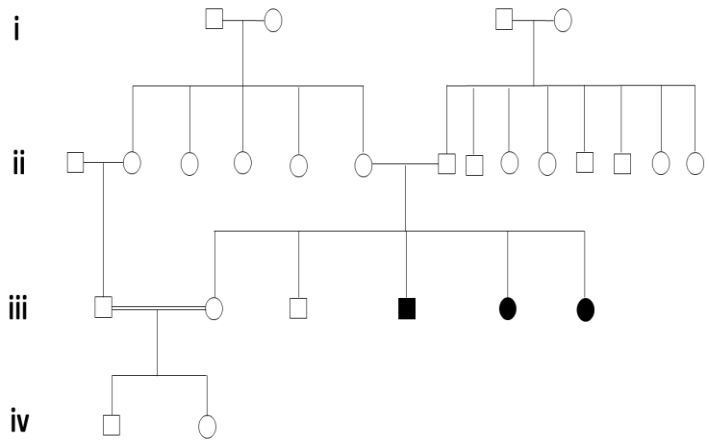


Figure 1:Pedigree Swl-Vil-MD-99L

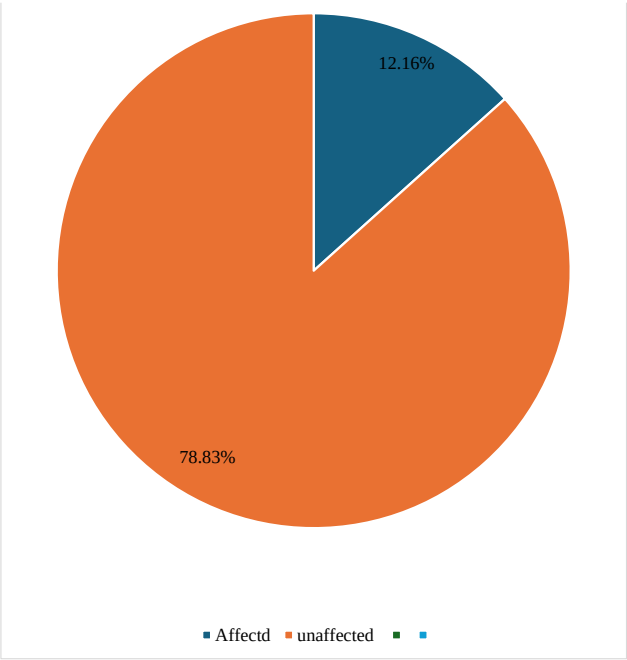


Figure 1: Pedigree SWL -VIL- MD-35-L Analysis

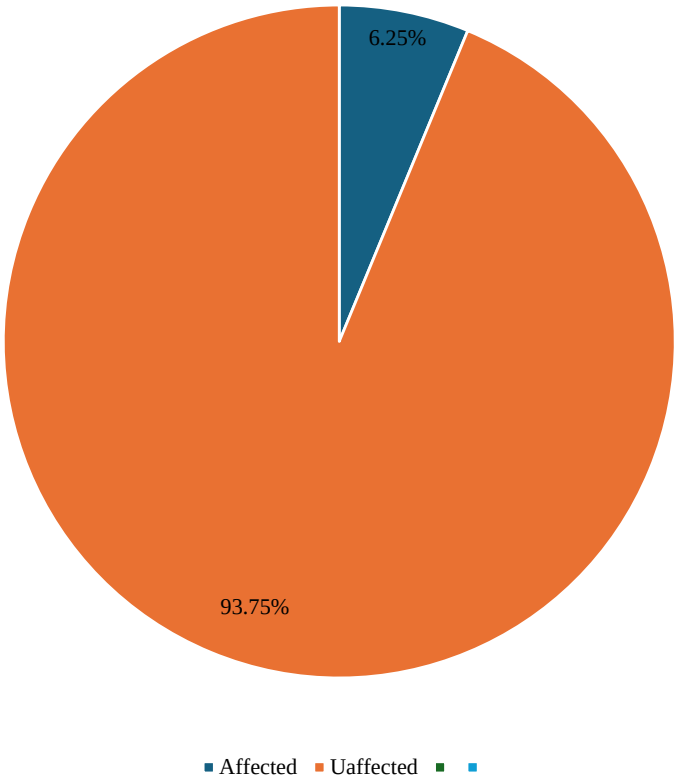


Figure 1:Pedigree SWL -VIL- MD-96-L Analysis

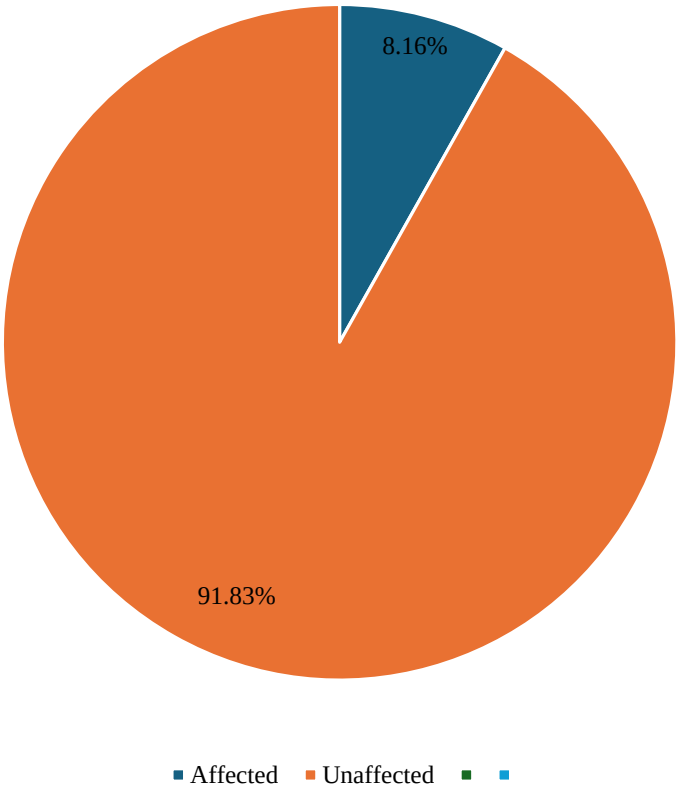


Figure 1:Pedigree SWL -VIL- MD-68-R analysis

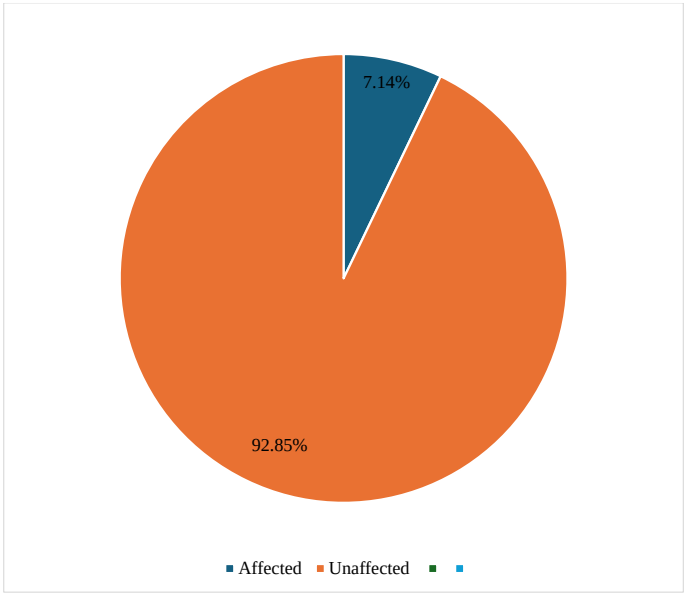
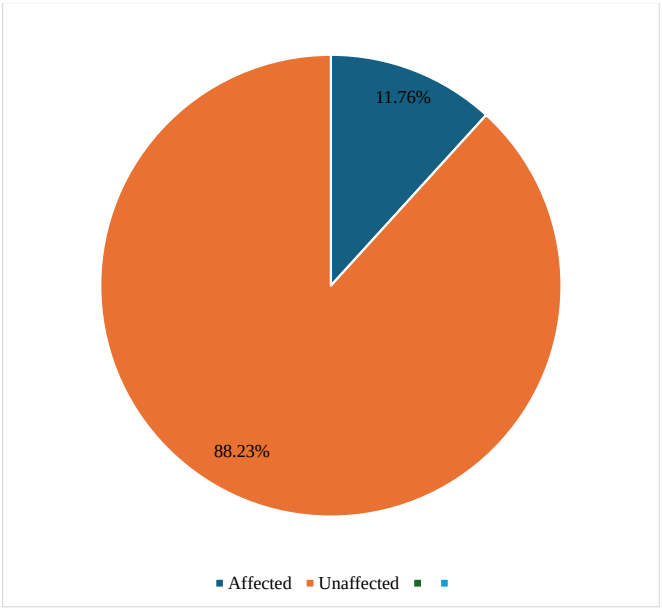


Figure 1:Pedigree Swl-CIT-MD-PC analysis



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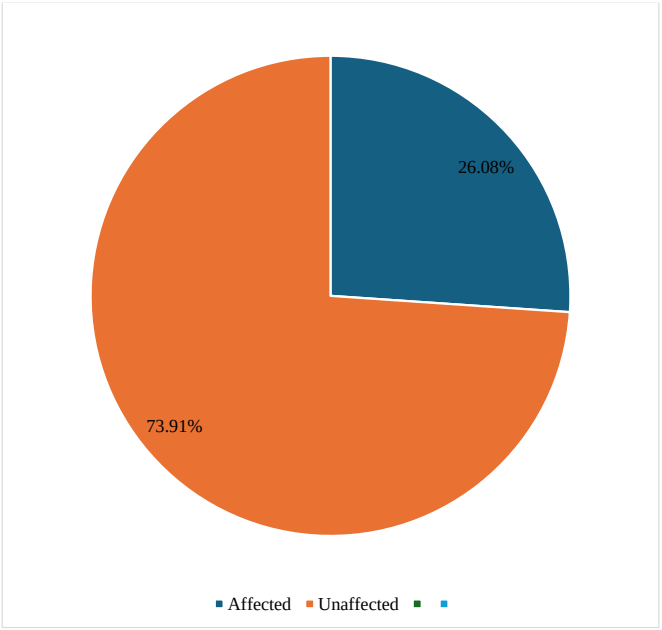

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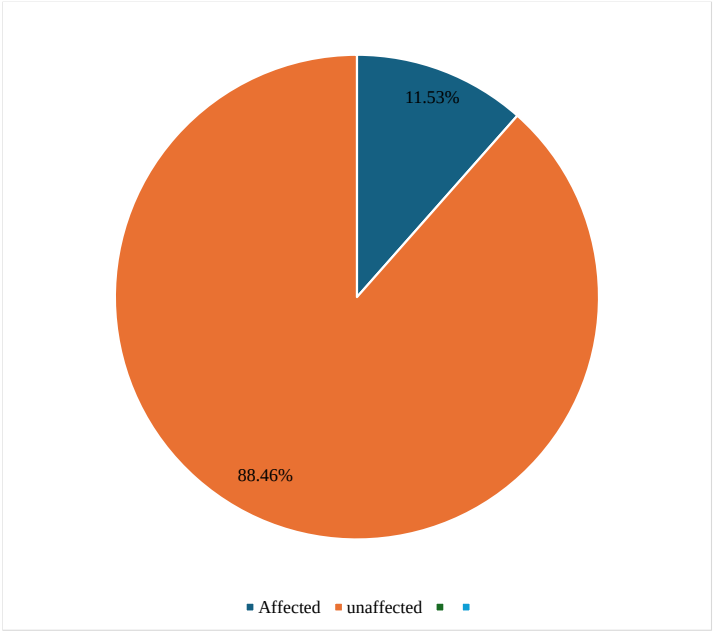

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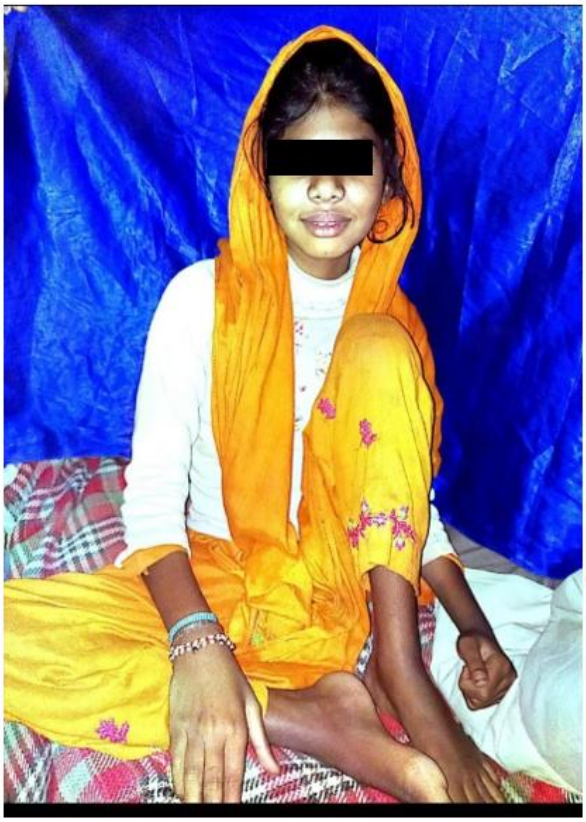

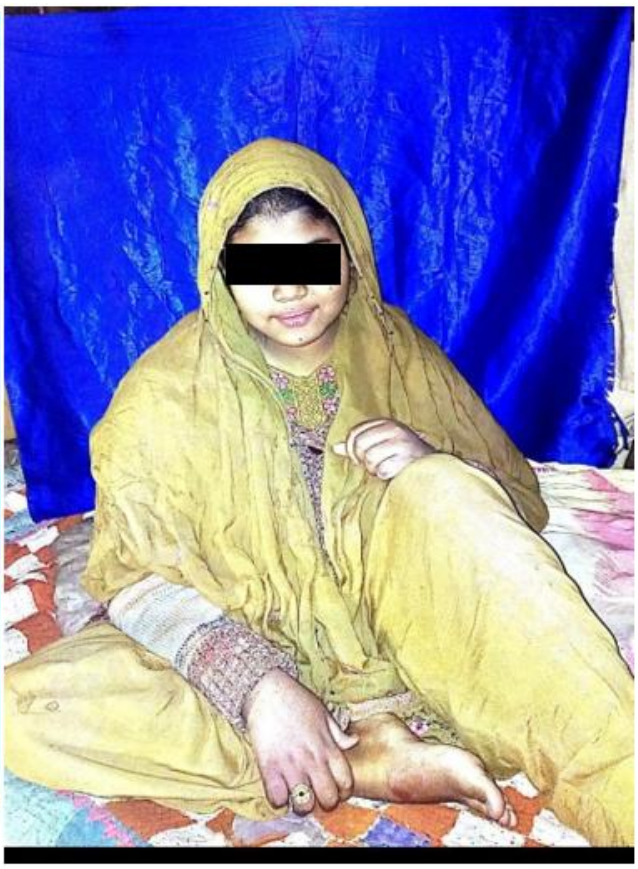

Family member no. B

Family member no. DF

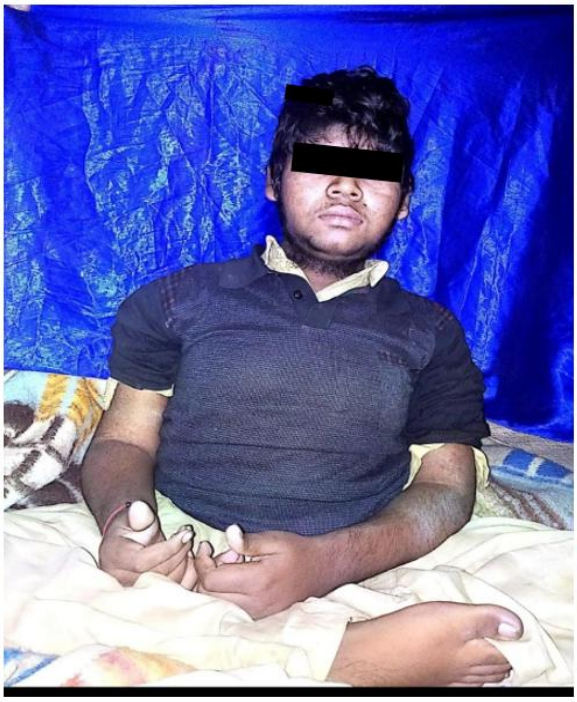

Figure 9: family member no. C

Family member no. B

Family member no. B

Family member no. A

Family member no. C

Family member no. A

Family member no. A

Family member no. A

Family member no. B

DISCUSSION

Muscular dystrophy comprises a group of hereditary disorders characterized by progressive muscle weakness and atrophy, with significant variations in onset, progression, and affected muscle groups. These conditions impact not only skeletal muscles but, in certain cases, also cardiac and respiratory muscles, leading to severe complications. While numerous genetic mutations have been identified as the underlying cause of various forms of muscular dystrophy, effective treatment remains elusive. The role of stem cell therapy and gene-targeted approaches has been explored extensively, yet clinical application faces substantial challenges, including immune response regulation and efficient delivery of therapeutic agents. Advances in the isolation of satellite cells and the use of specific growth factors have demonstrated potential in muscle regeneration, though their translation into effective treatments requires further investigation (24,25). The findings of this study revealed a muscular dystrophy prevalence of 10.25% among the selected families, with all affected individuals diagnosed with limb-girdle muscular dystrophy (LGMD). This differs from previous studies that reported varying prevalence rates and multiple forms of muscular dystrophy within a studied population (26). The exclusive presence of LGMD in the current study suggests a strong genetic predisposition, possibly influenced by consanguinity, which was present in 85.71% of the studied families. Genetic inheritance patterns, particularly autosomal dominant inheritance, were observed across multiple generations, aligning with previous findings that highlight the significant role of genetic transmission in LGMD cases.

A comparative analysis with previous research demonstrated similarities in phenotypic presentation, with affected individuals experiencing progressive weakness in the shoulder and pelvic girdle muscles. Cases examined in other studies reported early-onset difficulties in walking, climbing stairs, and maintaining balance, consistent with the findings of this study. However, a notable difference was observed in the mortality rate associated with respiratory complications, with one male individual succumbing to respiratory failure at the age of 16. This aligns with previous reports linking muscular dystrophy to progressive respiratory involvement, reinforcing the need for respiratory monitoring and early intervention in affected individuals (27). Prevalence variations between studies may be attributed to differences in population genetics, sample sizes, and diagnostic methodologies. While some studies identified LGMD as the predominant form of muscular dystrophy, others reported a more diverse range of muscular dystrophies, including Duchenne and Becker types, with mutations in different glycoprotein-related genes. The current study's exclusive focus on LGMD could be due to regional genetic factors or a limitation in the genetic analysis conducted. Additionally, previous research identified deficiencies in alpha-dystroglycan glycosylation as a major contributor to LGMD, whereas the genetic mutations in the current study remain unspecified. A more comprehensive molecular analysis could provide further insights into specific gene mutations responsible for the observed cases (28).

Pain and discomfort were reported in 39.28% of affected individuals, predominantly in the lower back, shoulders, hips, and legs. Previous research demonstrated similar trends, with a slightly higher prevalence of chronic pain in individuals with LGMD. The presence of muscle pain in this study supports the hypothesis that LGMD is not solely a degenerative disorder but also involves chronic musculoskeletal discomfort, which may contribute to functional decline. This finding highlights the necessity of pain management strategies in the long-term care of affected individuals (29). The study's strength lies in its detailed pedigree analysis and inclusion of both urban and rural populations, providing a broad representation of genetic inheritance patterns. However, limitations include a relatively small sample size, which restricts the generalizability of findings, and the lack of extensive genetic sequencing to confirm specific mutations. Additionally, environmental factors and lifestyle influences were not extensively examined, which could contribute to variations in disease progression among individuals (30). Future research should incorporate larger, more diverse populations to establish broader epidemiological trends. Genetic sequencing should be employed to identify precise mutations and potential genotype-phenotype correlations. Moreover, investigating potential therapeutic interventions, including physiotherapy and respiratory support, could offer practical recommendations for improving the quality of life in affected individuals. The role of consanguinity in increasing disease prevalence warrants further exploration to develop targeted genetic counseling programs aimed at reducing the incidence of inherited muscular dystrophies in at-risk populations.

CONCLUSION

This study examined the clinical and genetic aspects of muscular dystrophy within selected families in Division Sahiwal, highlighting the significant role of consanguinity in disease prevalence. The findings underscore the hereditary nature of the disorder, with limb-girdle muscular dystrophy being the predominant form observed. The study contributes to the understanding of genetic inheritance patterns and their implications for disease progression, emphasizing the need for early diagnosis, genetic counseling, and targeted

interventions. Raising awareness about the risks associated with consanguineous marriages is crucial to reducing the incidence of inherited disorders. Further genetic investigations, including exome sequencing, are recommended to enhance diagnostic accuracy and explore potential therapeutic approaches, ultimately improving disease management and patient outcomes.

AUTHOR CONTRIBUTIONS

Author	Contribution
Khawar Hayyat	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Abdullah*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Amir Anees	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Irshad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Iqbal Usama	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Saleem Khan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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