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On genotype-phenotype relationship of dystrophinopathies among Iranian population

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Keywords
Duchenne Muscular Dystrophy; Phenotype; Genotype; Dystrophin; Iran

Abstract

Background: Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are inherited X-linked disorders resulting from alterations in the dystrophin gene. Genotype-phenotype matching studies have revealed a link between disease severity, the amount of muscle dystrophin, and the extent of mutation/deletion on the dystrophin gene. This study aimed to assess the relationship between genetic alterations in the dystrophin gene and the clinical status of patients with dystrophinopathies among the Iranian population.

Methods: This cross-sectional study examined 54 patients with muscle weakness caused by abnormalities in the dystrophin gene at a hospital affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, in 2021. The participants' demographic information, including age, family history of muscle dystrophies, and family history of other medical diseases as well as the type of muscular dystrophy were recorded. Furthermore, the number and region of deleted exons based on dystrophy types were also evaluated using multiplex ligation-dependent probe amplification (MLPA). The patients' gaits were also assessed as using a wheelchair, the presence of waddling gaits, or toe gaits. The patients' clinical status and the coexistence of pulmonary, bulbar, and mental conditions were also examined and compared between the two groups of dystrophinopathies.

Results: In this study, 54 patients with dystrophinopathy with the mean age of 16.63 ± 12.10 years were evaluated, of whom 22 (40.7%) and 30 (55.6%) patients were classified as BMD and DMD, respectively.

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The most affected regions with deleted exons were exons 45-47 (n = 5) and 45-48 (n = 4) in patients with BMD, while exons 45, 48-52, 51-55, and 53 (2 cases per exon) were the most common affected exons in patients with DMD. Further analyses revealed that deletions in exons 45-47 and 51-55 were significantly associated with older and younger ages at the onset of becoming wheelchair-bound in patients with dystrophy, respectively. The hotspot range in both BMD and DMD was within exons 45-55 (n = 15 for each group); 63% of the patients had alterations on the dystrophin gene within this range [30 patients (68.18%) in the BMD group, 15 patients (53.57%) in the DMD group].

Conclusion: Exon deletion was the most common genetic alteration in patients with dystrophinopathies. No significant difference was observed between DMD and BMD regarding the number of deleted exons. Deletions in exons 45-47 and 51-55 were linked to later and earlier onset of becoming wheelchair-bound, respectively.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked disorder resulting from a genetic alteration in the dystrophin gene.[1] DMD primarily affects males with the onset of clinical symptoms at approximately 4 years of age.[2,3] Epidemiologic studies have estimated the prevalence of DMD to be about one in 3500-6000 live male births, indicating that DMD is the most common type of muscular dystrophy. Muscle dystrophin deficiency leads to the progressive degeneration of muscle fibers and muscle atrophy.[4] In patients with clinically severe DMD, large deletions (~two-thirds of cases) are more likely to be responsible for defective gene transcription, followed by small mutations in the remaining one-third of the dystrophic cases.[5] These genetic alterations result in a lack of dystrophin in almost all striated muscle cells. Beginning at about 3-5 years of age, the patient loses his/her ability to walk at the age of 9-12 years and becomes wheelchair-bound.[6] The mortality of these patients is usually followed by respiratory or cardiac muscle diseases occurring during the second or third decade of life.[7]

Becker muscular dystrophy (BMD) is an X-linked recessive inherited disorder characterized by slowly progressive muscle weakness.[8] BMD is less prevalent than DMD (one in 18500 live male births).[9]

Prolonged allelic DMD is the result of a mutation in the dystrophin gene, which does not affect its reading frame. While a complete dystrophin lack is observed in patients with DMD, varying degrees of functional reduction in dystrophin are observed in BMD cases.[10] Compared to the more severe clinical course of DMD, BMD is essentially a milder and more varied disorder. The mean age of onset usually is 12 years of age in patients with BMD; however, it can still appear in later life stages.[11] The ability to walk is often maintained up to 16 years of age, with a few patients experiencing a near-normal life with highly limited inabilities. The BMD mortality happens during the fourth or fifth decade of life, which is later compared to patients with DMD.[12] Despite milder musculoskeletal involvement, patients with BMD are at higher risk for developing cardiomyopathy, making heart failure the most common cause of mortality in these patients.[12]

Genotype-phenotype matching studies have revealed a link between disease severity, the amount of muscle dystrophin, and the extent of mutation/deletion on the dystrophin gene.[13] The normal or slightly reduced level of dystrophin is observed in clinically milder forms of dystrophy.[14] Identifying molecular genetic mechanisms leading to milder phenotypes or the link between a specific mutation and a particular clinical presentation is valuable because it can help researchers design novel gene therapy strategies. Deletions in dystrophin gene exons are the primary cause of DMD and BMD development.[2] The frameshift mutations can explain the difference between phenotypes in most cases. Frameshift mutation generates premature stop codon, leading to a complete lack of protein translation and dystrophin in muscular cells in DMD. In contrast, in the BMD cases, in-frame mutations are responsible for the development of the disease, allowing the production of diminished but still functional forms of dystrophin.[15]

The dystrophin gene is the largest known gene (2400 kb) on the human genome containing 79 exons with several alternative promoters and splice sites. Purine-rich sequences or exon detection sequences have been reported in some exons of this gene that may, as a cis element, allow the correct detection of exons.[16] Functional analyses have indicated that the Jagged1 overexpression improves the clinical severity of patients with dystrophy, offering Jagged1 as a potential candidate for the novel therapies of DMD in the dystrophin-independent methods.[17]

Although dystrophinopathies are well-known diseases in Iran, the genotype-phenotype relationship among the Iranian patients suffering from these diseases has not been extensively explored. This study aimed to investigate the relationship between genetic alterations in the dystrophin gene and their associated clinical abnormalities among Iranian patients with dystrophy.

Materials and Methods

This cross-sectional study was performed in 2021 at the Al-Zahra Hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. The present study included patients with muscle weakness caused by defects on the dystrophin gene. The study protocol was approved by the Research Committee and the Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1400.673).

Inclusion criteria were the presence of muscle weakness, confirmed genetic alterations on the dystrophin gene by multiplex ligation-dependent probe amplification (MLPA) genetic testing, and informed consent for participation in the study. Exclusion criteria were mortality during the study period, females with dystrophin gene alterations (carriers), absence of deletion or duplication on the genetic survey, and the need for further genetic assessments. All eligible patients meeting the inclusion/exclusion criteria in the concerned hospital from 2012 to 2020 were included in this study.

The patients' demographic data, age, family history of muscle dystrophies, and family history of other medical diseases were collected using a checklist. After evaluating muscle dystrophy type (DMD or BMD), the number and region of deleted exons were assessed. The patients' gaits were also assessed for using a wheelchair, presence of waddling gaits, or toe gaits. Besides, the patients' walking disturbance and falling history were evaluated. The presence of comorbid pulmonary conditions was assessed and the patients' intelligence quotient (IQ) levels were determined as well.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) software (version 25, IBM Corporation, Armonk, NY, USA). Quantitative and qualitative data were reported as mean ± standard deviation (SD) and frequency (percentage), respectively. Furthermore, independent t-test and chi-square test were used to analyze the nominal and categorical variables, respectively. In this study, $P < 0.05$ was considered as the significance level.

Results

Fifty-four patients with dystrophinopathy participated in this study. The patients' mean age was 16.30 ± 10.93 years with the range of 4-47 years. Eighteen patients (33.3%) had a positive family history of the dystrophic disease. Among patients with positive family history, 14 patients (77.8%), one patient (5.6%), and 3 patients (16.7%) had one, two, and three cases of dystrophinopathy in their families, respectively. Past medical history was positive in 9 patients (16.7%): seizures (n = 2, 3.7%), minor thalassemia (n = 1, 1.85%), autism (n = 1, 1.9%), attention deficit hyperactivity disorder (ADHD) (n = 2, 3.7%), and hypothyroidism (n = 1, 1.9%).

The genetic alterations were deletions in 52 patients (96.3%) and the duplication of exons 51 and 52 in two patients (3.7%).

As shown in table 1, the dystrophies were BMD in 22 patients (40.7%), DMD in 30 patients (55.6%), and intermediate in 2 patients (3.7%). Among cases with genetic deletions, 22 patients (42.3%) were patients with BMD, and 28 patients (53.8%) and two patients (3.8%) were DMD and intermediate types, respectively. Both cases (100%) with genetic duplications were suffering from DMD.

Table 2 presents the frequency distribution of deleted exons based on dystrophinopathy types. The hotspots of deletions in both BMD and DMD disorders were within the range of 45-55 exons with a frequency of 15 patients (68.18% for BMD and 53.57% for DMD) in each group. Moreover, both intermediate-type patients (100%) and both cases with duplications (100%) had alterations in this range.

Table 1. Frequency of types of genetic alteration in different types of dystrophinopathy

Genome dystrophinopathy	Deletion (n = 52) [n (%)]	Duplications (n = 2) [n (%)]	Total (n = 54) [n (%)]
BMD	22 (42.3)	0 (0)	22 (40.7)
DMD	28 (53.8)	2 (100)	30 (55.6)
Intermediate	2 (3.8)	0 (0)	2 (3.7)
Total	52 (100)	2 (100)	54 (100)

BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy

Table 2. Frequency distribution of deleted exons in patients with dystrophinopathy

Dystrophinopathy exons	BMD (n = 22)		DMD (n = 28)		
	n (%)	Number of deleted exons	Genome	n (%)	Number of deleted exons
4-9	1 (4.5)	6	1-4	1 (3.6)	4
12-44	1 (4.5)	33	3-12	1 (3.6)	10
16-44	1 (4.5)	29	5	1 (3.6)	1
17-43	1 (4.5)	27	8-12	1 (3.6)	5
24	1 (4.5)	1	8-13	2 (7.1)	6
42	1 (4.5)	1	8-25	1 (3.6)	18
45	1 (4.5)	1	17-43	1 (3.6)	27
45-47	5 (22.7)	3	20-29	1 (3.6)	10
45-48	4 (18.2)	4	23-55	1 (3.6)	33
45-49	1 (4.5)	5	31-41	1 (3.6)	11
45-55	1 (4.5)	11	45	2 (7.1)	1
46-52	1 (4.5)	7	45-49	1 (3.6)	5
48-51	1 (4.5)	4	45-51	1 (3.6)	7
51	1 (4.5)	1	45-53	1 (3.6)	9
57-79	1 (4.5)	23	46-55	1 (3.6)	10
Total	22 (100)	-	48-52	2 (7.1)	5
			49-50	1 (3.6)	2
			51-53	1 (3.6)	3
			51-55	2 (7.1)	5
			52-54	1 (3.6)	3
			53	2 (7.1)	1
			53-56	1 (3.6)	4
			57-79	1 (3.6)	23
			Total	28 (100)	

BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy

The highest frequency of deleted exons in this region was in patients with BMD in exons 45-47 (n = 5, 22.72%) and 45-48 (n = 4, 18.18%), while in patients with DMD, exons 45, 48-52, 51-55, and 53 were deleted with the frequency of two patients (7.14%) in each group of exons.

In the hotspot range, the highest number of deleted exons was 45-55 (11 exons) and 46-55 (10 exons) in patients with BMD and those with DMD, respectively. For the regions out of the hotspot range, there were 33 exons (12-44) and 33 exons (23-55) in BMD and DMD groups, respectively. In patients with intermediate dystrophinopathy, the deletions of exons 48-52 (5 exons) in one patient and exons 52-54 (3 exons) in another patient were noticed. Among all patients, duplicate exons (51 and 52) were found in only two patients with DMD.

In patients with deletions, 45 patients (86.5%) had < 20 deleted exons, and the other 7 patients (13.5%) had > 20 exons (large deletion). Among patients with > 20 exon deletions, 4 patients (57.1%) had BMD, and 3 patients (42.9%) were suffering from DMD. In patients with > 20 exon deletions, no statistically significant relationship was observed between the frequency distribution of deleted exons and the type of dystrophinopathy (P = 0.764) (Table 3).

Table 4 shows the distribution of gait frequency in patients with BMD and those with DMD regarding the deleted exons.

The wheelchair-bound patients' mean age was 27.80 ± 8.52 years (range: 19-40 years) in the BMD group; however, it was 9.27 ± 2.29 years (range: 4-13 years) in the DMD group. The mean age of wheelchair-bound patients was higher in patients with BMD (n = 4, 18.18%) than patients with DMD (4 cases, 14.28%).

Table 3. Number of deleted exons in different types of dystrophy

	Dystrophinopathy			Total [n (%)]	P
	BMD [n (%)]	DMD [n (%)]	Intermediate [n (%)]		
Exon deletion < 20	18 (40.0)	25 (55.6)	2 (4.3)	45 (86.5)	0.764
Exon deletion > 20	4 (57.1)	3 (42.9)	0 (0)	7 (13.5)	
Total	22 (42.3)	28 (53.8)	2 (3.8)	52 (100)	

BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy

Table 4. Frequency of gait disturbances in patients with Becker muscular dystrophy (BMD) and patients with Duchenne muscular dystrophy (DMD) based on their frequent exon deletions

Deleted exons	Dystrophy	Frequency	Falling (n)	Walking distance (n)	Toe gait (n)	Waddling (n)	Wheelchair (n)	Age of wheelchair-bound (year)
45-47	BMD	5	1	1	-	3	2	40.0
45-48	BMD	4	2	3	1	2	2	24.0
45	DMD	2	0	0	-	0	2	9.5
48-52	DMD	2	1	1	1	1	1	11.0
51-55	DMD	2	0	0	-	-	1	5.0
53	DMD	2	2	2	-	2	0	-

BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy

Out of 9 patients with BMD (40.9%) with gait disturbances, 3 patients (33.3%) had experienced falling, 4 patients (44.4%) had difficulties with walking, and one patient (11.1%) had toe gaits. Moreover, 5 patients (55.6%) had waddling gaits. On the other hand, 8 patients (28.6%) with DMD had gait disturbances. In these patients, 3 (37.5%), one (12.5%), and 3 (37.5%) cases had walking difficulties, toe gaits, and waddling gaits, respectively.

The clinical manifestations of patients with BMD and those with DMD regarding the most frequent exon deletions are shown in table 5. The age of onset in patients with DMD was lower compared to the patients with BMD. In the patients with BMD, family history was positive in 40% (2/5) of cases with 45-47 exon deletions, while 100% (4/4) of cases with 45-48 exon deletions had a family history of dystrophinopathies. Among patients with DMD, 100% of cases with 51-55 (2/2) and 53 (2/2) exon deletions were positive for family history. On the other hand, no patients with DMD with 45 (0/2) and 48-52 (0/2) exon deletions had a family history of dystrophies.

Low IQ was observed in one patient with BMD (4.5%) with deletions of exons 45-48 and one patient with DMD (3.3%) with deletions of exons 48-52. Most patients had not undergone cardiovascular evaluations due to the lack of clinical symptoms; hence, their cardiac analysis was unvalued. No bulbar or facial disorder was found in any research groups. A respiratory disorder was found in one patient with BMD (4.5%) with deletions on exons 45-48. Most paraspinal involvements were in the form of lordosis except for scoliosis in a patient with DMD (3.3%) with deletions on exons 48-52.

Discussion

In the present study, we evaluated 54 patients with muscle dystrophies. According to our findings, most cases had deletions in the dystrophin gene, and only two cases had duplications. We found no significant difference between DMD and BMD regarding the number of deleted exons.

Table 5. Part I: Clinical symptoms of patients with Becker muscular dystrophy (BMD) and patients with Duchenne muscular dystrophy (DMD) based on frequent exon deletions

Deleted exons	Dystrophinopathy	Frequency	Mean age at onset (year)	Family history (n)	Low IQ (n)
45-47	BMD	5	10.2	2	-
45-48	BMD	4	8.7	4	1
45	DMD	2	6.0	-	-
48-52	DMD	2	3.5	-	1
51-55	DMD	2	3.5	2	-
53	DMD	2	0.6	2	-

Table 5. Part II: Clinical symptoms of patients with Becker muscular dystrophy (BMD) and patients with Duchenne muscular dystrophy (DMD) based on frequent exon deletions

Deleted exons	Lung (n)	Bulbar (n)	Ocular (n)	Paraspinal (n)	Facial (n)
45-47	-	-	-	Lordosis (3)	-
45-48	1	-	-	Lordosis (4)	-
45	-	-	-	-	-
48-52	-	-	-	Lordosis (1), lordosis and scoliosis (1)	-
51-55	-	-	-	Lordosis (2)	-
53	-	-	-	Lordosis (1)	-

BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy; IQ: Intelligence quotient

Moreover, deletions on exons 45-47 were associated with the higher age of wheelchair dependency, while patients with deletions on exons 51-55 reached the status of wheelchair-bound at lower ages. Furthermore, patients with 45-47 exon deletions had higher age of onset, while patients with 53 exon deletions had lower age of onset. Spinal disorders were also more likely observed in cases with 45-47 and 45-48 exon deletions among patients with BMD.

Several papers have explored the phenotypes of DMD or BMD in different populations. In 2018, Mori-Yoshimura et al. evaluated 192 Japanese patients with BMD and assessed their phenotypes regarding the deleted exons. They reported that 45-47 exon deletion was the most common genotype and patients with 45-49 exon deletions developed gait disturbances earlier than other cases.[18] This evidence highlights the importance of genetic alterations and their associated phenotypes in different populations. According to our findings, patients with deletions in exons 51-55 were younger when they became wheelchair-bound.

Okubo et al. in Japan reviewed data from 1497 patients with dystrophinopathies. According to their research, exon deletion was found in 91% of patients, most frequently in exons 45-52.[19] Moreover, Suh et al. reported the rates of deletions and duplications in 130 Korean patients as 71.8% and 16.4%, respectively.[20] Their findings were similar to the present findings and those reported in Western countries.[21-23] To the best of our knowledge, the reported ratios have been consistent in recent articles. The importance of our study is that we evaluated patients' phenotypes regarding their genotypes. The findings highlight the importance of epidemiologic data in this regard.

In 2021, Yun et al. studied 227 patients and reported that progressive skeletal muscle weakness, elevated serum creatine kinase (CK) levels, scoliosis, dilated cardiomyopathy, and respiratory discomfort were the most common clinical signs in patients with dystrophy. It was also reported that patients with deletions in exons 51-55 were younger when they became wheelchair-bound.[24] These findings are in line with our findings.

According to Lim et al.,[25] mutations altering the C-terminal domain are linked to a decline in wheelchair use in their cohort of patients with DMD. A similar association was discovered in mutations affecting the Dp116 and Dp71 isoforms. Age exhibited an odds ratio (OR) > 1.75 across all models with wheelchair use as the indicated outcome (P = 0.005); however, body mass index (BMI) and steroid use were not significant predictors. Only mutations affecting the Dp140 isoform demonstrated a significant connection when cardiomyopathy status was used as an outcome. BMI and steroid use were not significant predictors of cardiomyopathy status, and age generated an OR of at least 1.31 (P = 0.0005). These findings were not observed or addressed in the present study.

According to our findings and the existing literature, evaluating patients' genotypes would provide beneficial information about the possible phenotypes of patients in different populations. Accordingly, further studies are recommended to address this issue.

One of the limitations of this study was the retrospective design of the study. This issue may miss potential confounding factors because the data were previously gathered for clinical and therapeutic indications, which usually do not include data required for specific research purposes. Essentially, levels of evidence in retrospective studies are lower compared to prospective studies. The second limitation was a relatively small sample size; hence, future researchers should include larger sample sizes to reach more definite and comprehensive findings.

Conclusion

Exon deletion was the most common genotype in the patients with dystrophy, and no significant difference was observed between DMD and BMD regarding the number of deleted exons. Deletions in exons 45-47 and 51-55 were linked to later and earlier onset of becoming wheelchair-bound, respectively. Further studies on larger populations in Iran are recommended.

Conflict of Interests

The authors declare no conflict of interest in this study.

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