Muscular Dystrophies

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Abstract. Muscular dystrophies are a heterogeneous group of inherited disorders characterized by progressive muscle wasting and weakness. Majority of genes and their protein products responsible for the dystrophies have been identified in recent years. Using molecular studies, now it is possible to establish a precise diagnosis, provide prognosis, detect preclinical cases, identify carriers, and offer prenatal diagnostic testing. Molecular genetic approaches also seem to offer the best prospect for developing effective treatments in the future. **[Indian J Pediatr 2004; 71 (2) : 161-168]**
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DEFINITION OF MUSCULAR DYSTROPHY

The muscular dystrophies are a group of inherited disorders characterized by progressive muscle wasting and weakness.[1] Muscular dystrophy includes many genetically distinct disorders. The list of causative genes for muscular dystrophies has been expanding rapidly, including those for congenital muscular dystrophies. Although clinical signs and symptoms are important but immunohistochemical and DNA based mutation analysis have made it possible to establish precise diagnosis of the dystrophies. Most of the dystrophies unfortunately have a very poor prognosis; therefore genetic counseling based on reliable prenatal diagnosis, and carrier detection can be useful in providing help to the affected families.

Duchenne/Becker dystrophy (D/BMD) is the commonest form of hereditary muscular dystrophy. Using positional cloning approaches, search for the gene responsible for the disease resulted in the discovery of the protein 'dystrophin'. The protein was found to be deficient or absent in D/BMD patients. Further studies showed that dystrophin and its associated proteins form a multimeric complex which plays crucial role in stabilization of sarcolemmal membrane[2] (Fig. 1). The importance of the complex can be gauged from the fact that as many as eight hereditary muscular dystrophies result due to mutations in the dystrophin complex. In addition, several other genes have been identified which are defective in other muscular dystrophies.

CLASSIFICATION OF MUSCULAR DYSTROPHIES[3]

General classification is still based on clinical signs and symptoms while immunohistochemistry and gene studies

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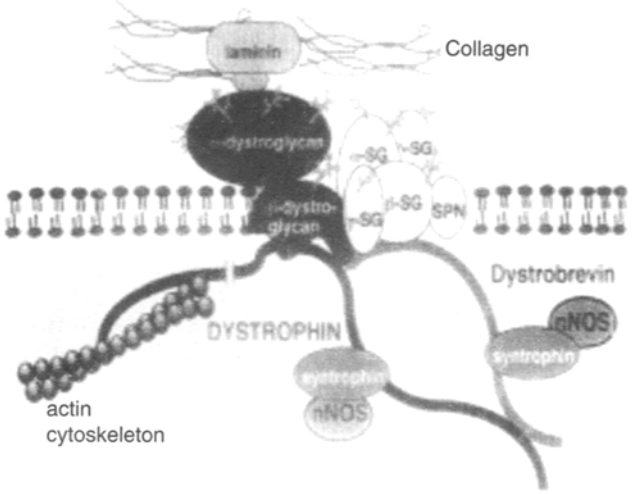

Fig. 1. Schematic Diagram of the Dystrophin Complex

are useful for subtyping.

1. Duchenne and Becker Muscular Dystrophy
2. Emery-Dreifuss Muscular Dystrophy
3. Limb-Girdle Muscular Dystrophy
4. Congenital Muscular Dystrophies
5. Distal Myopathies
6. Facioscapulohumeral Dystrophy
7. Oculopharyngeal Dystrophy
8. Myotonic Dystrophy
9. Hereditary Inclusion Body Myopathies

1. Duchenne and Becker Muscular Dystrophies (Dystrophinopathies)

Duchenne and Becker are allelic disorders. DMD is a disease of muscle that becomes evident in early childhood but BMD is milder with late onset.[4] The disease is inherited as an X-linked recessive trait and predominantly

affects boys. Weakness is progressive affecting mainly the proximal limb musculature which causes most of the boys to start using wheelchair by age 12 and die in their late teens or early twenties from respiratory and cardiac failure. BMD is clinically similar but milder, with onset in the teenage years or early 20s. Loss of ability to walk may occur later and many individuals survive into middle age and beyond (Table 1). The gene for D/BMD located on Xp21 locus is 2.5 Mb in length, consisting of more than 85 exons of mean size 0.2 kb, introns of mean size 35 kb and the gene is transcribed into a 14 kb mRNA. DMD may occasionally present at birth as hypotonia, or later failure to thrive or delay in learning to walk. The earliest manifestations of the disease are an inability to run properly and a tendency to walk on the toes due to shortening of the Achilles tendons. An important early sign is an inability to rise from the floor or a chair without pressing on the thighs (Gower's sign). The DMD patients without clinically remarkable calf hypertrophy can be diagnosed by the presence of the valley sign or Pradhan's sign.[5,6] Abnormalities of dystrophin protein are a common cause of the muscular dystrophy and testing for dystrophin gene has become a part of routine diagnostic evaluation of patients who present with progressive proximal muscle weakness and high serum creatine kinase concentrations.

Deletions of one or more exons of dystrophin gene account for 55-65% of cases of D/BMD which tend to be clustered (hotspots) in two regions of the gene and "multiplex PCR" is a rapid, efficient and practical, most widely available method for screening for such mutations.[7,8] It can detect about 98% of deletions. However, approximately 30% of the cases are not due to gene deletion or duplication. In such cases a point mutation can be suspected but their detection is much more difficult in the clinical setting. For research purposes SSCP analysis has been successful in screening for point mutations followed by automated sequencing. Recently, a single condition amplification/internal primer (SCAIP) method has been developed that allows sequence analysis of the dystrophin gene in a rapid and economical fashion.[9]

Using multiplex PCR, if a deletion is present in an affected individual (proband), it becomes a marker for the family which can be used for prenatal diagnosis (PND) in that particular family. In cases where no deletion is detected, linkage studies based on CA repeat analysis[10] can be performed to assess the carrier status of females in the family as well as PND. Microarray based mutation analysis for D/BMD are still under development.[11]

Prevention of DMD is possible with counseling and prenatal diagnosis. Since the disorder is inherited through female carriers, identification of such carriers is an essential aspect of genetic counseling. Microsatellite markers (CA repeats) are used for the establishment of carrier status of female relatives of affected boys or known carriers and prenatal diagnosis.[12,13] The only limitation of CA repeat analysis is that it depends on linkage which might be subject to errors due to recombination. The DMD locus is so large that markers lying at the two extremes themselves show a recombination frequency of 0.12.[14] The use of multiple markers reduces such errors. Higher than expected rates of germline mosaicism and incidence of *de novo* mutations should also be taken into consideration for genetic counselling.[15] Prenatal diagnosis can be achieved by DNA studies on chorionic villi sample at around 10-11 weeks of gestation or from cultured amniotic fluid cells at around 16-18 weeks gestation. The strategy for PND has been illustrated.[16] Many laboratories in India have established molecular techniques for mutation detection, carrier analysis, and prenatal diagnosis in DMD.[12,13,17] The molecular basis of two allelic forms D/BMD has been explained by frameshift hypothesis. The correlation between genotype (reading frame) and phenotype (clinical severity) showed a higher number of DMD patients (~20%) deviating from this hypothesis.[18,19] A high frequency of new or *de novo* mutations in D/BMD patients have been reported.[15,20] Earlier, dystrophin staining with monoclonal antibody could be used for differential diagnosis of patients with muscular dystrophies in India.[21]

Cardiac changes often culminating in cardiac failure are at times a dramatic cause of death in patients of DMD. The profile of electrocardiographic changes in DMD was studied by Bhattacharya *et al.*[22] The phenotype of cases with deletion of single exons did not differ significantly from those with deletion of multiple exons. However, the distribution of deletions in different countries was variable. Population-based variations in frequency and distribution of dystrophin gene deletions were studied in North Indian DMD patients by Singh *et al.*[23] Banerjee and Verma[24] observed that there is likely to be no ethnic difference with respect to deletions in the DMD gene. However, recently, a study of the deletion status in South Indian patients suggested variations of exonic deletions in the southern and northern populations of India.[25]

One third of DMD patients suffer moderate to severe nonprogressive form of mental retardation. Although novel dystrophins have been identified in brain, however CNS phenotypes are not solely determined by mutations of the dystrophin gene alone. It is proposed that interactions of dystrophin with other genes may also play an important role in DMD linked mental retardation.[26-29]

2. Emery-Dreifuss Muscular Dystrophy (EDMD)

Emery-Dreifuss muscular dystrophy has a highly characteristic phenotype and varied inheritance. All three, X-linked, autosomal recessive and autosomal dominant forms are recognized, and the genes involved encode proteins which are components of the nuclear envelope. The gene involved in XLEDMD is emerin and that involved in AD and AR EDMD is lamin A/C.[43] The age of onset, symptoms etc have been elaborated (Table 1).

Table 1. Types of Muscular Dystrophies

Disease	Prominent clinical features	Incidence	Mode of inheritance	Gene locus & Size	Molecular Diagnosis	Treatment
Duchenne's dystrophy (DMD)	Onset : 3-5 y Proximal muscle weakness and wasting, difficulty doing sit-up, calf hypertrophy, Gower's and Pradhan sign present, wheelchair bound by 12 y, CPK 15,000-20,000 IU/L	1:3500 male newborns	X-linked recessive	Xp21, 2.4 Mb, >85 exons codes for dystrophin	Multiplex PCR for detection of deletion(s), CA repeat analysis for carrier detection and PND, dystrophin immunostaining	Genetic counseling and prenatal diagnosis
Becker's dystrophy (BMD)	Onset:5-15y. Exertional cramps and myalgia, CPK 5000-7000 IU/L, Less severe	1:3500 male newborns	X-linked recessive	Xp21, 2.4 Mb, >85 exons codes for dystrophin	Multiplex PCR for detection of deletion(s), CA repeat analysis for carrier detection and PND, immunostaining for dystrophin	Genetic counseling and prenatal diagnosis
Emery-Dreifuss muscular dystrophy (EDMD)	Onset in childhood or adolescence. Early onset joint contractures affecting elbows and ankles. CPK normal or moderately elevated	1:100,000	X-linked recessive	Xq28 Codes for emerin	Immunostaining of muscle or skin tissue for emerin, immunoblot analysis in WBCs	Identification of cardiac conduction abnormalities, Pacemaker
Limb Girdle muscular dystrophies (LGMD)	Onset variable for different types, Calf hypertrophy, calpain 3-deficient patients have consistent calf muscle contractures, 2B type with proximal and distal weakness, CPK elevated		Different types and Genetic classification shown in Table 2			Pacemaker or heart transplant
Congenital muscular dystrophies (CMD)	Onset in infancy, central nervous system affected		Different types and Genetic classification shown in Table 3			
Distal Myopathies	Onset variable according to type		Different types and Genetic classification shown in Table 4			
Facioscapulohumeral dystrophy (FSHD)	Age of onset usually 21, proximal facial weakness, shoulders sloped and rotate anteriorly, CPK 5 times normal	1:20,000 3rd most common	Autosomal dominant	Short 4q35 fragment i.e. <35kb (normal is >300 kb)	variable size deletion of a 3.3 kb repetitive DNA sequence	
Oculopharyngeal dystrophy (OPMD)	Onset 30-50y, extraocular muscle weakness, facial and chewing muscles, CPK normal or mildly elevated		Autosomal dominant	14q11, polyadenylate binding protein 2 gene, PABP2	Expansion of GCG repeat within PABP2 gene, patients have 8-13 repeats; normal: 6 repeats	Eyelid crutches or surgery
Myotonic dystrophies (DM) DM Type 1	Onset before age 50, in adolescence, weakness & stiffness in distal limb muscles, facial & axial muscles, CPK normal or mildly elevated.	15: 100,000		19q13.3	Expanded CTG repeat, >1000 CTG repeats in DMPK protein kinase gene, normal: 5-37 repeats	Cataract surgery treatment of hyoersimnia, sleep apnea, pacemaker
DM Type 2 (PROMM)	Onset before age 20, muscle stiffness, proximal muscle weakness, CPK elevated 10 times normal				CCTG expansion, ~5000 repeats in intron 1 of zinc finger protein 9 (*ZNF9*) gene	
Hereditary inclusion body myopathies (h-IBM)	Onset between 10-30y, involvement of distal lower limbs, reflexes diminished, CPK normal or mildly elevated		Autosomal recessive, few dominant	9p1-q1		

3. Limb Girdle Muscular Dystrophy

The limb girdle muscular dystrophies (LGMDs) are clinically and genetically heterogeneous group of progressive disorders of skeletal muscle with a primary or predominant involvement of the pelvic or shoulder-girdle musculature. The clinical course is characterized by normal intelligence but there is a great variability depending on age of onset. Severe forms have onset in the first decade and rapid progression while milder forms have late onset and a slower course.[30] So far 15 genes, 5 autosomal dominant (AD) and 10 autosomal recessive (AR) responsible for LGMD have been mapped as shown in Table 2. Less than 10% of cases are inherited as an autosomal dominant trait and are relatively mild but all other cases are inherited as autosomal recessive trait, often more severe affecting both males and females. One subtype (1B) may be allelic to autosomal Emery-Dreifuss dystrophy. LGMD2A or calpainopathy is the most frequent form of LGMD caused by a specific protease (calpain 3) deficiency, while 4 other recessive subtypes have been found to be caused by deficiencies of particular sarcoglycans (dystrophin associated glycoproteins) which form part of the dystrophin associated protein complex of muscle membrane. The AR-LGMDs have been recently reviewed by Zatz *et al.*[31]

The deficiency of the 50kDa dystrophin-associated-glycoprotein (adhalin) in autosomal recessive limb girdle muscular dystrophy (LGMD or a-sarcoglcanopathy) patients in India was first reported by Handa *et al*[32] while severe childhood autosomal recessive muscular dystrophy (SCARMD) classified as adhalinopathy was described by Dua *et al.*[33]

4. Congenital Muscular Dystrophies

The congenital muscular dystrophies (CMD) are autosomal recessively inherited heterogeneous group of

Table 2. Limb-girdle Muscular Dystrophies

Type and common name	Prominent clinical features	Age of onset	Mode of inheritance	Gene location	Gene product
LGMD1A	Slow progression, late loss of ambulation	Young adults	Autosomal Dominant	5q22-34 Myotilin	
LGMD1B	Weakness symmetric, proximal lower limb, slow progression , upper limbs involved by 3rd-4th decade	< 20 years	Autosomal Dominant	1q11-21	Laminin A and C
LGMD1C	Weakness: moderate, proximal, cramps after exercise, calf hypertrophy	5 years	Autosomal Dominant	3p25	Caveolin-3
LGMD1D	Calf hypertrophy occasional, slow progression, patients remain ambulatory	2nd decade & later	Autosomal Dominant	6q22	
LGMD1E	Proximal weakness, no associated systemic problems	Young adult life	Autosomal Dominant	7	
LGMD2A	Heterogeneous severity, mild phenotype, asymptomatic with elevated CK levels, inability to walk on heels, loss of walking, mean age 17 (5-39 yrs)	2-40 yrs, median=14	Autosomal recessive	15q15 CAPN3	Calpain 3
LGMD2B	Leg weakness, loss of ambulation >30 yrs, hypertrophy is uncommon	12-39 years	Autosomal recessive	2p13	Dysferlin
LGMD2C	Severe childhood autosomal recessive (SCARMD), respiratory failure in 3rd decade, muscle hypertrophy	Mean 5 years	Autosomal recessive	13q12	Gamma-sarcoglycan
LGMD2D	Proximal weakness more than distal, calf hypertrophy in some patients, elevated CK	2-15 years	Autosomal recessive	17q12 Adhalin	Alpha-sarcoglycan
LGMD2E	Severe, mild phenotype, proximal weakness, muscle hypertrophy	< 3 years to teens	Autosomal recessive	4q12	Beta-sarcoglycan
LGMD2F	Proximal weakness, calf hypertrophy, wheelchair bound 9-16 years	2-10 years	Autosomal recessive	5q33	Delta-sarcoglycan
LGMD2G	occasional calf hypertrophy, myopathy and weakness in arms: proximal, legs: proximal & distal	12.5 years	Autosomal recessive	17q11	Telethonin
LGMD2H	Proximal weakness, back pain, fatigue, slow progression	8-27 years	Autosomal recessive	9q31-33	Trim32
LGMD2I	Weakness and wasting of shoulder girdle muscles, slow progression, primary restrictive respiratory and cardiac involvement, elevated CK	2nd, 3rd decade	Autosomal recessive	19q13.3	Fukutin-related protein (FKRP)
LGMD2J	Tibial muscular dystrophy, severe childhood-onset-LGMD	35-45 years (AD)	Autosomal recessive		Titin

diseases, presenting at birth or within the first few months of life with hypotonia, muscle weakness, contractures, and motor development delay. Various forms of CMD have been classified in Table 3. A proportion of children with CMD show an absence or marked deficiency in an extracellular matrix protein, merosin[39] which divide CMD into 2 groups: merosin-negative and merosin-positive. Recently, post translation modification of proteins has been defined as a new area of focus for muscular dystrophy research by the identification of a group of disease genes that encode known or putative glycosylation enzymes. Walker-Warburg Syndrome (WWS) and muscle-eye-brain disease (MEB) are caused by mutations in 2 genes involved in O-mannosylation, POMT1 and POMGnT1 respectively. Fukuyuma muscular dystrophy (FCMD) is due to mutations in fukutin, a phospholigand transferase. CMD type 1C and LGMD2I are allelic, due to mutations in fukutin-related protein (FKRP). A deficiency in post-translational modification of alpha-dystroglycan is a common feature of all these muscular dystrophies.[40]

5. Distal Muscular Dystrophies

Distal myopathies affect predominantly the distal musculature without the noticeable involvement of other muscle groups. Many individuals are only mildly affected, although some may ultimately develop serious problems in walking and everyday life. For many years only one form was recognized in Sweden by Welander. Several different types of distal muscular dystrophies have been described (Table 4).

6. Facioscapulohumeral Muscular Dystrophy

Fascioscapulohumeral muscular dystrophy (FSHD) is clinically highly variable, since it can present in an early onset or infantile form. The essential clinical features are weakness of the facial, scapulohumeral, anterior tibial and pelvic girdle muscles including retinal vascular disease, sensory hearing loss and in severe cases, even abnormalities of the CNS. Recently, Pradhan[41] from SGPGIMS has described a new clinical sign in FSHD patients. This sign is a particular bulge or depression over the neck, shoulders and arms termed as "poly-hill sign". The sign has high diagnostic utility as it is present even when facial muscle involvement is doubtful or when the lower limbs are more significantly involved.[41]

FSHD is an autosomal dominant muscle disease, for which molecular genetic testing has become the diagnostic tool of choice. At least 95% of families with FSHD show linkage to chromosome 4q35.[42] Although the FSHD gene has not yet been cloned, the demonstration of a disease-associated deletion of an integral number of copies of a tandemly repeated 3.3 kb sequence on chromosome 4q35 can be used in diagnosis of FSHD with high specificity and sensitivity. This deletion is predicted to exercise its disease causing effect by altering expression of other genes on chromosome 4q.

7. Oculopharyngeal Muscular Dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is unusual amongst other forms of muscular dystrophy in that its presentation is often in very late adult life typically in the 6th decade. The symptoms are progressive ptosis and dysphagia which is followed by involvement of other cranial and limb muscles. OPMD is inherited as autosomal dominant condition and a single mutation type is present with an expanded GCG repeat detectable in the polyA binding protein 2 gene.[44] The gene associated with the disease is located on chromosome 14 (Table 1).

8. Myotonic Dystrophy

Myotonic dystrophy (DM) presents a variety of clinical and genetic problems. It has a range of severity and age of onset, from birth to old age together with the involvement of numerous systems. The distribution of muscle involvement is characteristic, and the combination of myotonia with significant weakness and wasting leads to

TABLE 3. Congenital Muscular Dystrophies

Type	Prominent clinical features	Age of onset	Mode of inheritance	Gene location	Gene product
Laminin α2 chain (merosin) deficiency	Hypotonia, delayed early motor milestones greater proximal than distal weakness	At birth or few months after	Autosomal recessive	6q22-23 LAMA2	Laminin α2 chain
α7 Integrin deficiency	Extremely rare		Autosomal recessive	12q13 ITGA7	α7 Integrin
Fukuyama muscular dystrophy (FCMD)	delayed milestones, severe muscle weakness, mental retardation	Common in Japan (7-12 in 100,000), early onset	Autosomal recessive	9q31-33 Fukutin	Fukutin
Walker-Warburg syndrome (WWS)	Muscular dystrophy, eye and brain malformations	Early onset, 2-6 months	Autosomal recessive	POMT1	unknown
Muscle-Eye-Brain disease (MEB)	Severe muscle weakness, profound mental retardation, poor vision, early death	Early onset, 2-6 months	Autosomal recessive	POMGnT1	unknown

a confident diagnosis of myotonic dystrophy. The facial muscles, sternomastoids and distal limb muscles are usually the earliest to be affected, exhibiting a pattern differing from most other neuromuscular disorders. Two types of myotonic dystrophies have been described (Table 1). Although DM most commonly presents in adolescence or adult life, but it may also occur in neonates and young children who show marked clinical differences. The hallmarks of the congenital form are generalized hypotonia and facial diplegia, jaw weakness, respiratory and feeding difficulty and mental retardation.

There is usually an unstable CTG trinucleotide repeat at 19q13.3. An expansion of this CTG repeat in the 3' UTR region of the DMPK (myotonic dystrophy protein kinase) gene has been identified as specific for DM Type 1. In normal individuals, there are 5-37 CTG repeats, but repeat expansion occurs in the myotonic dystrophy, a longer repeat correlates with more severe disease (Table 1). The expanded repeats may result in major structural changes in DNA with the formation of "hairpin" bends.[34] Congenital myotonic dystrophy is usually associated with >1000 CTG repeats. Although the CTG expansion had been identified and found to be responsible for almost all cases of myotonic dystrophy, another common myotonic disorder was identified, proximal myotonic dystrophy (PROMM).[35] This disorder is relatively mild and slowly progressive. DM2 is caused by a CCTG expansion (~5000 repeats) located in intron 1 of the zinc finger protein 9 (*ZNF9*) gene (Table 1). Another form, myotonic dystrophy type 3 resembling the classical form of myotonic dystrophy is under study whose gene is still unknown.

A study on the expansion of CTG repeat in myotonin protein kinase gene in DM patients from India was first reported by Basu *et al.*[36,37] The frequencies of haplotypes based upon the (CTG)n repeat and three other biallelic markers in and around the myotonic dystrophy (DM) locus were estimated in ethnically, linguistically and geographically diverse sub-populations of India.[38] Extensive variation in frequencies of large (CTG)n alleles (> or=18 repeats) was found in normal Indian population.

9. Hereditary Inclusion Body Myopathies

Hereditary inclusion body myopathies (h-IBM) are autosomal recessive forms (AR) and begins between ages 10 and 30. Sporadic IBM usually begins after age 50. Autosomal dominant forms are less common where the pattern varies and distal muscles are sometimes involved. A limb-girdle distribution is the most common. In the AR forms, there is preferential involvement of distal lower limbs often present with foot drop. Proximal arm muscles and neck flexors may be affected later. AR h-IBM has been mapped to the same locus as Nonaka distal myopathy i.e. 9p1-q1 (Table 1).

THERAPEUTIC APPROACHES IN MUSCULAR DYSTROPHY

Most patients suffering from muscular dystrophies can be provided precise diagnosis of the underlying defects, but

Table 4. Distal Myopathies

Type and common name	Prominent clinical features	Age of onset inheritance	Mode of location	Gene location	Gene product
Late adult-onset type 1 (Welander)	Weakness in distal upper extremeties affecting finger and wrist extensors	After age 40	Autosomal Dominant	2p13	possibly dysferlin
Late adult-onset type 2 (Markesbery-Griggs/Udd)	Weakness of toe and foot, later finger and wrist extensors, proximal upper and lower limb weakness occur	After age 40	Autosomal Dominant	2q31	Titin
Early adult-onset type 1 (Nonaka)	Begins with ankle and toe dorsiflexors, early distal upper limb and later proximal weakness	Late teens or 20s	Autosomal recessive or sporadic	9p1-q1	Unknown
Early adult-onset type 2 (Miyoshi)	Weakness begins in posterior compartment, difficulty in climbing stairs and standing on toes, proximal lower and upper limb weakness, wheelchair bound within 10 years	Between ages 15-30	Autosomal recessive or sporadic	2p13	Dysferlin
Early adult-onset type 3 (Laing)	Weakness in anterior compartment and neck flexors, later finger extensor and shoulder girdle weakness	Between ages 4-25	Autosomal Dominant	14q11	
Distal myopathy with vocal cord and pharyngeal weakness	Distal upper and lower limb weakness, later vocal cord and pharyngeal weakness	Begins age 30-60	Autosomal Dominant	5q31	
Myofibrillar (desmin) myopathy	Accumulation of desmin in muscle fibres, weakness in hands and distal lower limbs, Respiratory insufficiency	Any age, usually 25-45	Autosomal Dominant or sporadic, recessive X-linked	11q21-23 2q35 12	αb-crystallin Desmin

there is no efficient treatment to prevent disability and death. The palliative treatments currently in use can only help to slow the functional impairment for a short time. For last several years, attempts are being made to look for novel therapeutic approaches. Presently, three main approaches are being explored: pharmacological therapy, cell therapy and gene therapy.[45] The pharmacological therapy involves the use of novel steroids and anabolic agents which may slow the progression of the disease. So far, clinical trials using such agents showed poor or negative results.

Cell therapy involves implantation of donor cells into the host. For muscle diseases, the donor cells are either myoblasts (myogenic-cell) or pluripotent stem cells. In animal models, transplantation of myoblasts (MT) into *mdx* mouse (animal model for Duchenne muscular dystrophy),[46] *dy/dy* mice (model for merosin-related muscular dystrophies)[47] and SJL mouse (dysferlin-related muscular dystrophies)[48] have been able to restore expression of normal proteins. However, the problem of acquiring large pool of satellite cells and need for long-term immunosuppression still limit its utility in humans.[49]

As most of the muscular dystrophies are caused by single-gene defects, genetic therapy, involving replacement or modification of a gene seems to be a promising approach. Gene therapy for Duchenne muscular dystrophy (DMD) serves as a model for development of therapies for other types of dystrophies.[50] Major limitation of the therapy is the large size of the gene. Therefore, efforts have been made for improved gene therapy by developing (*i*) newer vectors, (*ii*) mini-gene cassettes and (*iii*) antisense/interfering RNA therapies. Non-viral vectors for gene transfer, targeted gene modification and transcription modulation are also being explored. It has been observed that the expression of an agrin mini-gene cured merosin-deficient congenital muscular dystrophy in mice.[51] Recently, the delivery of functional mini- and micro-dystrophins by recombinant rAAV vectors, therapeutic antisense-induced exon skipping and dystrophin replacement by utrophin (functionally homologous to dystrophin) upregulation have been shown to have several advantages.[52]

It is expected that some of these approaches will be useful to provide efficient tools for the ultimate clinical goal: to prolong function and life in severe muscular dystrophy patients. However, since all these methodologies are in early experimental stages, there is still scope for pharmacological therapeutical approaches.

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