Research Paper Medical Science

# Recent Genetic Advances In Becker' S Muscular Dystrophy

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**ABSTRACT**

Muscular dystrophies are progressive hereditary disorders causing muscular weakness which in turn occurs due to gradual break-down of muscle fibers and their replacement with fibro fatty tissue.
Amongst thes ,Duchene Muscular Dystrophy (DMD) and Becker's Muscular Dystrophy (BMD)are caused by mutation in the dystrophin gene , the largest gene identified in humans, which encodes the protein dystrophin .Both of these are inherited as X linked recessive disorder. BMD is a less severe form than DMD, with late onset and slower progression.
Accuracy of diagnosis of these entities has improved alot with the recognition of dystrophin gene defect &dystrophin staining of muscle biopsy.
Recently, combination of stem cell transplantation and gene therapy afford promising results in treatment of BMD, this is further reinforced after seeing immense improvement intwo young patients from Mumbai who have been treated with stem cell implantation in February 2013.

**KEYWORDS** Muscular Dystrophy, Dystrophin , X LinkedRecessiveDisorder, Gene therapy, Stem Cells, Follistatin.

## INTRODUCTION

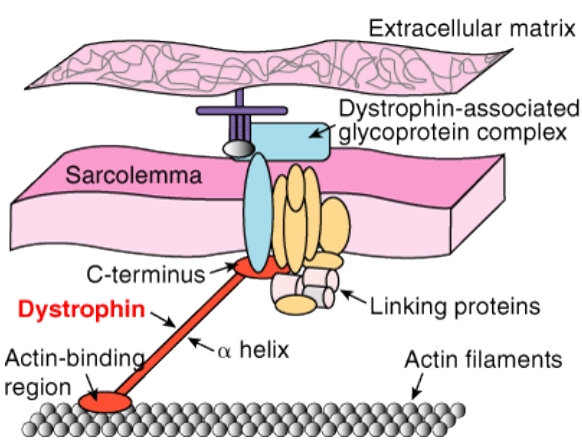
Duchenne (DMD) and Becker muscular dystrophies (BMD) result from abnormal or absent dystrophin, and hence these conditions are classified as dystrophinopathies (8).

The incidence and prevalence of BMD are lower than those of DMD.

The estimated incidence of BMD is 1 in 30,000 males as compared to DMD in which it is 1 in 3500 at birth.(4).

Surprisingly, in BMD incidence of cardiac involvement is invariably more pronounced than skeletal muscle weakness(17) .

## THE DYSTROPHIN GENE &ITS FUNCTIONS




Dystrophin gene situated on short arm of X chromosome, in region 2, band 1[X p 21] provides instructions for making a protein called dystrophin..It has a length of 24 kb .It has a DNA length of 2.5Mb.It consists of 79 exons that form a 14 Kb mRNA transcript.The protein dystrophin accounts for .002% of a striated [skeletal] muscle cell's protein.

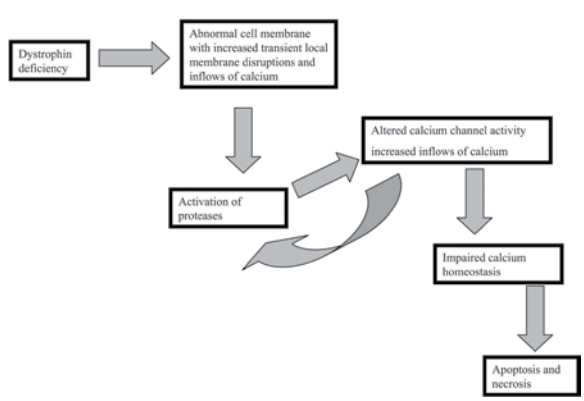
The large size of this gene makes it susceptible to a high mutation rate [10-4 /loci/generation](2).

## SIGNIFICANCE OF DYSTROPHIN

In a myocyte, the proteinDystrophin is responsible for

1. Actin-binding
2. Maintaining the structural integrity of muscle tissue
3. Localization of the sarcolemmal neuronal nitric oxide synthase which contributes to the fine-tuning of muscle blood flow during physical activity.
4. Chemical signaling within cells.
5. Without dystrophin, muscle cells cannot form the dystrophin–glycoprotein complex (DGC), and degenerate as a result of mechanical stress during contraction (3).

## PATHOGENESIS OF BMD

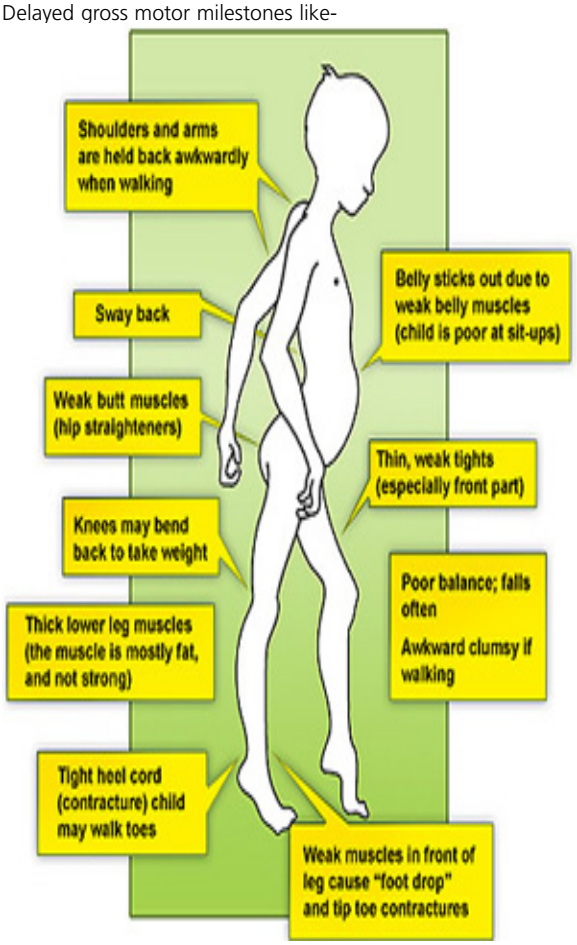


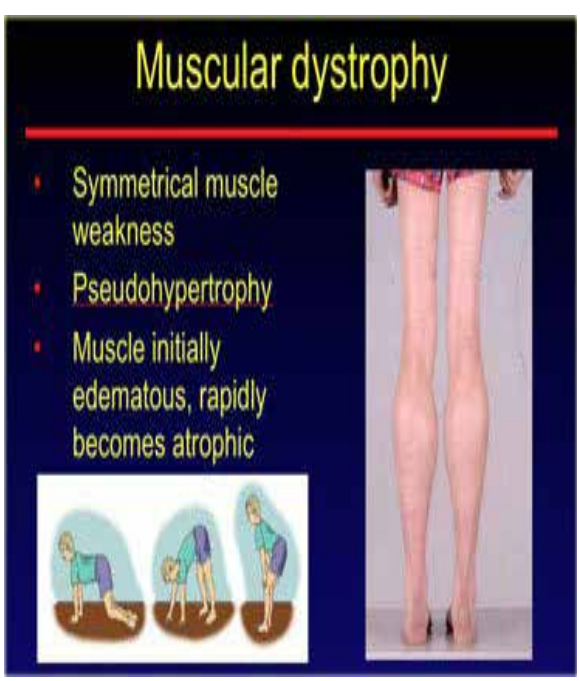

Mutations in the DMD gene alter either the structure or function ofdystrophin .Muscle cells without enough of this protein become damaged as muscles repeatedly contract and relax with use. The damaged fibers weaken and die over time, leading to the muscle weakness and heart problems characteristic of Duchenne and Becker muscular dystrophies.

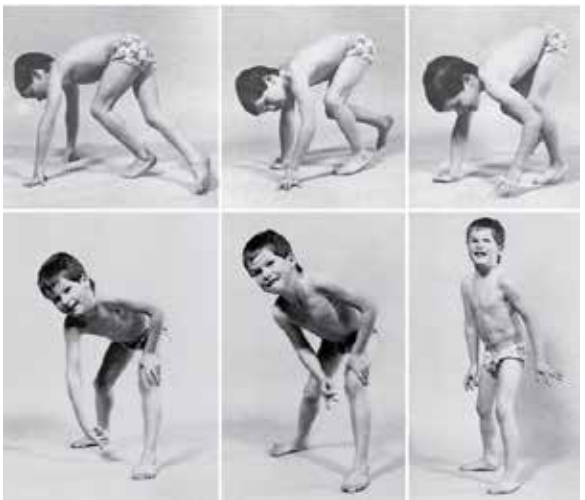
Mutations that lead to an abnormal version of dystrophin that retains some function usually cause Becker muscular dystro-

phywhile mutations that prevent the production of any functional dystrophin tend to cause Duchenne muscular dystrophy(14).

**CLINICAL PRESENTATION**
**DEVELOPMENTAL HISTORY OF THE CHILD**
Delayed gross motor milestones like-



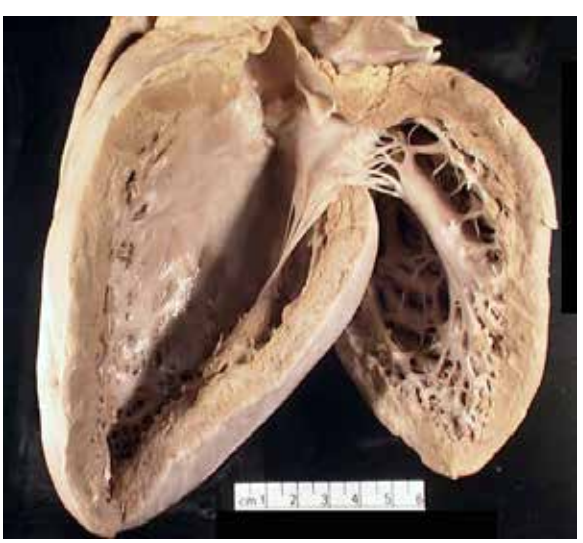



- Toe -walking also known as equinus.
- Proximal muscle weakness, clumsiness.
- Difficulty in breathing.
- Skeletal deformities of chest and back region such as scoliosis.
- Gower sign in which there is difficulty in rising up from the floor is not very conclusive but it does point out to proximal weakness in the hip extensors, leading to the pattern of movement seen when patients rise from the floor.
- Progressive muscular weakness in the leg and pelvis more severe than in the arms &neck .
- Muscle deformities- painful contractions of heels, legs, psuedohypertrophy of calf muscles.
- Fatigue.
- Sometimes isolated weakness of the quadriceps femoris muscle could be the only presenting symptom. (1), (10).

**CARDIOMYO PATHY IN BMD**

- It has been observed that cardiomyopathy is seen as the most prominent feature associated with BMDto such an extent thatit can be the only presenting symptom without any muscular weakness. (7), (13), (15),(17).



**DIAGNOSIS:**
**The condition is diagnosed by –**
1. Pedigree analysis
2. Laboratory investigations

**1. PEDIGREE ANALYSIS**
As stated already BMD is a X linked recessive disorder in which female is the carrier, and males are usually affected by the disease.

**1. FAMILY HISTORY**

a. A thorough family historyis the most important step to establish the diagnosis as BMD is a X linked Recessive disorder. In this type of genetic disorderthe female is usually unaffected and is said to be a carrier of the disorder.

A carrier mother has a 50% chance of passing the gene defect in each pregnancy in such a way that her 50% sons who inherit the mutation will be affected and 50% daughters who inherit the mutation will be carriers. Siblings of the proband are at risk of transmitting the gene defect based on the carrier status of the mother. Varying levels of dystrophin in a woman are the result of random inactivation of X chromosome which is also called as Lyonization.

An isolated proband with no family history could be the result of de-novo mutation. (13), (16).

The carrier status of the female could be of two types

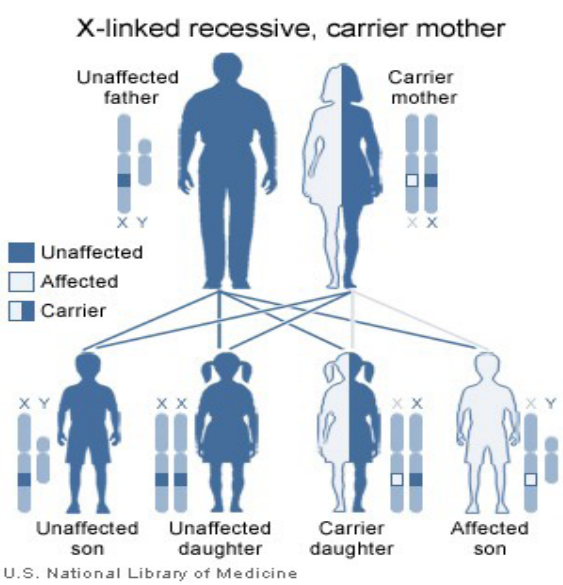
**A. Obligate** carrier if she has-

1. Affected father
2. An affected son and one affected relative in her maternal line.
3. Two affected sons without significant maternal history

**B.Possible** carrier if she has

1. One or more affected relatives in her maternal line.
2. Only one affected son and no other relative with the disorder.

**PEDEGREE CHART**




**2. LABORATORY INVESTIGATIONS**

- Serum Creatine Kinase [SCK] Levels-

Moderate-to-severe elevation (that is, 5-100 times the normal level).

Normal level ofS C K
Males
6-11 years: 150-499 U/L
12-17 years: 94-499 U/L
> or =18 years: 52-336 U/L
Females
6-7 years: 134-391 U/L
8-14 years: 91-391 U/L
15-17 years: 53-269 U/L
> or =18 years: 38-176 U/L

Note: Strenuous exercise or intramuscular injections may cause transient elevation of SCK (3).

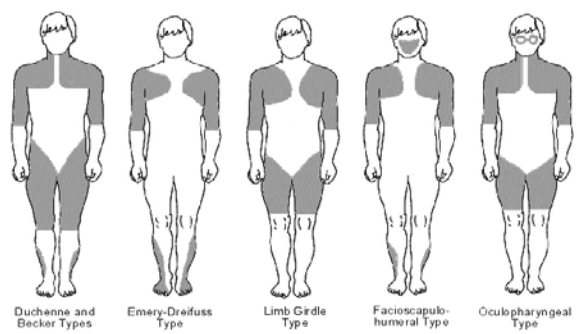
- Muscle biopsy with Dystrophin Antibody Staining
- Liver Function Test for aspartate transaminase and alanine transaminase
- Muscle biopsy &Standard histology-
- Electrocardiogram/echocardiogram- to diagnose cardiomyopathy
- Pulmonary Function Tests–for assessing respiratory stress and/ or failurecaused by progressive weakness of respiratory muscles.

**3. CYTOGENETIC STUDIES :**

- Dystrophin gene deletion analysis–

To see specific exon deletions using the multiplex polymerase chain reaction, southern blot analysis, and Fluorescent In Situ Hybridization [FISH](3

**DIFFERENTIAL DIAGNOSIS**




**Main areas of muscle weakness in different types of dystrophy**

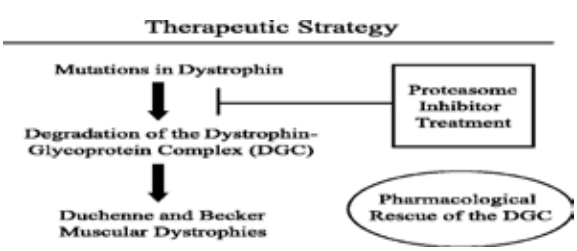
**MANAGEMENT & TREATMENT**

As such no permanent cure exists for BMD, hence the treatment is focused on controlling a patient's symptoms and addressing the occupational and recreational needs of the patient.

It includes the following modalities(12).

**1. MEDICINAL TREATMENT**

Recently medicinal treatment aims at targeting the primary genetic defect, that is the dystrophin mutation. It includes pharmacological administration of histone deacetylase inhibitors or nitic oxide donors or to reconstruct the DGC complex by up-regulation of related proteins like Utrophins(8).




**2. GENE THERAPY**

Dystrophin deficient myopathies are the most common genetically determined skeletal muscle diseases. In gene therapy , the objective is to reconstitute the dystrophin gene expression by gene transfer through differerent vectors like adenoviruses (Ad), retroviruses, adeno-associated viruses (AAV) and plasmids (9). Recently it is found that AAV serotype8 is most efficient for gene delivery in the skeletal as well as cardiac muscle. However the AAVs are equally capable of producing complications related to immune responses and cannot be administrated to the patients who are already immunized against the natural virus (6).

Gene therapy also aims at endogenous gene repair by exon skipping, in which vectors expressing small riboproteins that target the mutated exons &form a shorter but in- frame transcript that is translated into functional dystrophin. (5),(8).

**3.FOLLISTATIN**

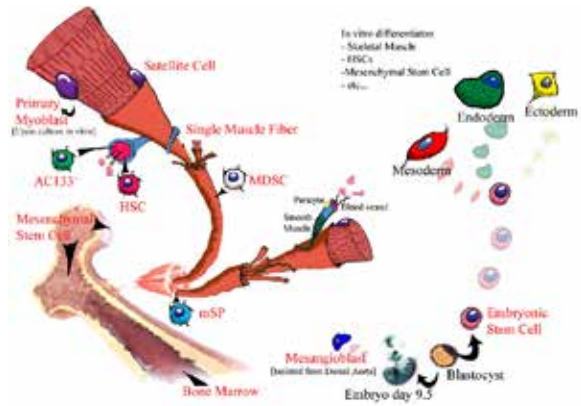
The current research focuses on the use of for treating muscular dystrophies. Follistatin is an antagonist of Myostatin , which is a member of the transforming growth factor beta family and it is a negative regulator of muscle development. Deletion ofthe myostatin gene from mdx mice significantly enlarged the muscle mass and increased strength and performance.

Notably, the development of antibodies that specifically target and inhibit myostatin led to

functional improvement of dystrophicmuscle in mice raising thepossibility that myostatin blocking therapies may represent an alternative to gene replacement.

In this regard, the study published in PNAS by Haidetet al(8 )describes the beneficial effect of different myostatin-binding proteinsdelivered by one-time postnatal intramuscular injection of AAV vectors to mdx mice. It is noteworthy that Follistatin generates the FS-344 and FS-317 isoforms by alternative splicing. By subsequent cleavage FS-344 and FS- 317 give rise to FS-315 and FS-288 polypeptides respectively; FS-315 is found in the circulation, whereas FS-288 exhibits high tissue affinity and may decrease reproductive ability because it locates in the gonads and interferes with pituitary follicle-stimulating hormone. Interestingly, in the study by Haidet et al.(8) the expression of the FS-344 isoformand its derivative FS-315 did not affect fertility neither were found histological alterations in the gonads. In addition, an increase in the muscle mass was observed both in the directly injected muscles and in surrounding tissues, suggesting a potential paracrine effect of the circulating isoform. Unfortunately,it was not determined whether the FS-344follistatin isoform had any positive effect on heart function or any negative effects on distal organs, such as liver and brain.

**4. STEM CELL BASED THERAPIES**




Stem cell populations with myogenic potential can be derived from multiple regions of the body at various stages of development as shown in above figure .The chosen cell type to be successful it must be optimized to deal with the survival,localization, and immunogenicity.

Out of all these cell types, mesangioblast are seen to fulfilmajority of the criterias & can thus be used in the treatment of muscular dystrophies .

Mesangioblasts serve as a paradigm for widespread distribution, and upon growth factor pre-treatment are able to correct significantly the dystrophic phenotype and serve as a beacon of hope for patients suffering from various muscular dystrophies.

Recently, in February 2013, two young patients from Mumbai have shown immense improvement after stem cell implantation(11).

**CONCLUSION**

Thus it is clear from above discussion that Becker's Muscular Dystrophy is the milder variant of Duchene Muscular Dystrophy , resulting due to in frame mutation of the gene Dystrophin. The diagnosis of the condition at molecularlevel is certainly improved by the newer modalities like Multiplex Polymerase chain reaction.The treatment is multifaceted which focuses on medicinal therapy, gene therapy, stem cell therapy , use of myostatin antagonists etc.followed by rehabilitation therapy that addresses the physical, occupational and recreational needs of the patients . Complete cure in near future can be expected with greathopeby using gene therapy and implementation of stem cells& the use of Follistatin.

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