

MUSCULAR DYSTROPHIES: CONTEMPORARY VIEWS ON THE DEVELOPMENT OF THE DISEASE

Malika Shuhratovna Hojimatova

Abstract: Muscular dystrophies are hereditary disorders primarily affecting skeletal muscles. Several distinct types of the disease are recognized, the majority of which are caused by mutations in genes encoding structural or regulatory proteins of muscle cells. Today, modern genetic approaches to therapy have demonstrated promising results.

Keywords: Muscular dystrophies, Duchenne, Becker, Myotonic dystrophy

Introduction

Muscular dystrophies represent a heterogeneous group of inherited disorders of skeletal musculature characterized by progressive muscle weakness, degeneration of myofibrils, and replacement of muscle tissue with connective and adipose tissue. These diseases differ in age of onset, rate of progression, distribution pattern of muscle involvement, and mechanisms of genetic inheritance. In most cases, mutations in genes encoding structural or regulatory muscle proteins underlie the disease. The overall epidemiological burden and clinical manifestations vary depending on the dystrophy type.

Major Clinical Forms and Classification

The most studied and clinically significant forms include:

- 1) Duchenne and Becker muscular dystrophies (DMD/BMD): Caused by mutations in the DMD gene encoding dystrophin, predominantly affecting males. DMD presents in early childhood and progresses rapidly.
- 2) Limb-girdle muscular dystrophies (LGMD): A heterogeneous group comprising dozens of genetic subtypes (over 20 known genes), classified as dominant or recessive. Clinically, the proximal muscles of the pelvic and shoulder girdle are primarily involved.
- 3) Myotonic dystrophy types 1 and 2 (DM1, DM2): Multisystemic disorders caused by trinucleotide or tetranucleotide repeat expansions, characterized by pronounced myotonia, muscle weakness, and systemic involvement.
- 4) Facioscapulohumeral muscular dystrophy (FSHD): Associated with deregulation of the DUX4 gene, leading to asymmetric atrophy of facial and scapulohumeral muscles.

In addition, rarer forms exist (embryonic types, dystrophies linked to sarcoplasmic or nuclear proteins), each with unique genetic and pathogenetic mechanisms.

Genetics and Molecular Pathogenesis

Muscular dystrophies encompass a wide range of genetic mechanisms, including nucleotide deletions, duplications, point mutations, repeat expansions, and epigenetic dysregulation.



- **DMD/BMD:** Loss or reduction of dystrophin function disrupts the dystrophin–glycoprotein complex, increasing sarcolemmal fragility during mechanical stress, causing calcium influx and subsequent myocyte necrosis.
- **LGMD:** Mutations affect sarcoglycans, sarcomeric proteins, mitochondrial function, or protein aggregation control, leading to muscle fiber degeneration in specific anatomical patterns.
- **DM1/DM2:** RNA toxicity due to expanded repeat transcripts accumulating in the nucleus and sequestering splicing factors (e.g., MBNL proteins), results in widespread splicing dysregulation and multisystem pathology.
- **FSHD:** Epigenetic derepression of the *D4Z4* locus allows aberrant expression of *DUX4* in myocytes, activating embryonic gene programs and inducing myotoxicity.

Clinical Manifestations and Natural Course

Early symptoms of DMD include frequent falls, difficulty walking, and pseudohypertrophy of the calf muscles. The disease progresses to loss of independent ambulation in early adolescence, followed by respiratory and cardiac involvement. BMD presents later and progresses more slowly. LGMD forms range from rapidly progressive childhood variants to milder adult-onset cases.

DM1 is characterized by myotonia, cataracts, cardiac conduction defects, and endocrine disturbances. FSHD typically presents with asymmetric weakness of the face and shoulder girdle muscles.

Diagnosis

The diagnostic algorithm includes:

1. **Clinical assessment:** Pattern of weakness, age of onset, and family history.
2. **Laboratory markers:** Elevated creatine kinase (CK) levels, particularly in DMD.
3. **Electromyography (EMG):** Reveals a myopathic pattern.
4. **Muscle MRI:** Visualizes fatty replacement and distribution of affected muscles (especially useful for LGMD and FSHD).
5. **Genetic testing:** Molecular confirmation of causative mutations (e.g., *DMD* deletions/duplications, repeat expansions in DM1/DM2, NGS panels for LGMD) — the gold standard for diagnosis.
6. **Muscle biopsy:** Histological and immunohistochemical evaluation, performed when genetic testing is inconclusive.

Current Treatment and Management

The cornerstone of management is multidisciplinary supportive care: physiotherapy, orthopedic correction, respiratory therapy (including ventilation support when necessary), cardiological monitoring and treatment, metabolic and endocrine correction, and psychological and social support.

Specific Pharmacological and Genetic Approaches

- Glucocorticoids (e.g., prednisone, deflazacort) have shown efficacy in slowing disease progression in DMD.



- Antisense oligonucleotides (ASO, exon skipping): Aim to restore the reading frame of the *DMD* gene. Several ASO therapies (e.g., eteplirsen) have received conditional approval, though their long-term efficacy and safety remain under investigation.
- Gene therapy (AAV-mediated delivery of micro/mini-dystrophin): Programs such as SRP-9001 (delandistrogene moxeparvovec) show promising biomarker and functional results but have raised safety concerns. In 2024–2025, reports of severe hepatic complications and fatalities following AAV therapies led to regulatory reviews and temporary suspensions, underscoring the need for careful risk–benefit assessment.
- RNA toxicity-targeted therapy in DM1: Early trials of ASO, RNAi, and small molecules demonstrate encouraging preclinical and phase 1 results but are not yet available for clinical use.
- FSHD (*DUX4* targeting): Experimental therapies aim to suppress *DUX4* transcription or translation; several candidates are in clinical or preclinical development.

Challenges and Limitations

1. **Genetic heterogeneity:** The multiplicity of causative genes (especially in LGMD) complicates the creation of universal therapeutic approaches and requires personalized medicine strategies.
2. **Safety of gene and vector therapies:** Recent serious adverse events highlight the necessity of strict patient selection, dose optimization, and long-term monitoring.
3. **Limited efficacy in advanced disease:** Most gene therapies are effective only before significant fatty replacement of muscles; regeneration of lost tissue remains a major obstacle.
4. **Need for large-scale clinical trials:** Due to disease rarity and phenotypic variability, multicenter studies and validated surrogate endpoints (biomarkers, MRI patterns, functional measures) are crucial.

Future Directions

- Optimization of **AAV vectors** with improved muscle tropism and reduced systemic dosage; combination therapies integrating gene replacement and immunomodulation.
- Development of safer and more effective **ASO conjugates** (e.g., peptide-linked ASO) for DMD, DM1, and FSHD.
- **Regenerative medicine approaches** (stem cell therapy, growth factors) remain at the experimental stage.
- Establishment of **global registries and research consortia** to standardize outcome measures, enhance statistical power, and facilitate data and biospecimen sharing.

Conclusion

Muscular dystrophies constitute a complex group of genetically determined disorders with diverse clinical manifestations. Over the past decade, significant progress has been achieved in understanding molecular mechanisms and developing targeted therapies such as ASO and AAV-based gene therapies. However, critical challenges remain — including therapy safety, limited effectiveness in advanced stages, and the need for long-term randomized studies. A multidisciplinary approach, early genetic diagnosis, and participation in international registries are essential to accelerate translation of scientific advances into clinical practice.

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