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# Dystrophin and Beyond: A Review of Genetic Landscape of Duchenne Muscular Dystrophy

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***Abstract*: *Duchenne muscular dystrophy (DMD) is a very severe, progressive, and lethal disease of skeletal muscle degeneration, respiratory complications, and cardiomyopathy. The identification of the dystrophin gene requires an understanding of the muscle protein and its working mechanism. The learnings from decades of research in life sciences could establish the functionalities of dystrophin in striated muscle. Here, we discuss the pathophysiological basis and the recent advancement of DMD towards the therapeutic approaches that are currently close to or are under ongoing clinical trials in humans. We attempted to summarise the current understanding of DMD – the dystrophin glycoprotein complex and chronic inflammation. Understanding the complex pathophysiology of DMD is crucial for the development of effective treatment and adds hope to the ongoing experimental research.***

***Keywords*: *AAV, Dystrophin, Duchenne muscular dystrophy, Review.***

***Abbreviations:***
DGC: Dystrophin-Glycoprotein Complex
DMD: Duchenne Muscular Dystrophy
AAV: Adeno-Associated Viruses
NT: N-Terminal
NHEJ: Non-Homologous End Joining
HDR: Homology-Directed Repair
CVS: Chorionic Villus Sampling
NIPT: Noninvasive Prenatal Testing
CK: Creatine Kinase
Aos: Anti-Sense Oligonucleotides
EMG: Electromyography
DAPC: Dystrophin-Associated Glycoprotein Complex
ECM: Extracellular Matrix
ITRs: Inverted Terminal Repeats
HDR: Homology-Directed Repair
NHEJ: Non-Homologous End Joining
Cas: CRISPR-Associated Endonuclease

## I. INTRODUCTION

In the 19th century, muscular dystrophy gained recognition as a primary disease affecting the muscles. Duchenne Muscular Dystrophy is a differentiated muscular dystrophy wherein muscle weakness is secondary to disease of motor neurons and their roots. DMD comes from a family of muscle diseases, which are called fatal muscle-wasting diseases. This affects approximately 1 in 5,000 male births [1]. The nature of this progressive X-linked disease is degenerative, making the patients bound to a wheelchair at an early age [2]. DMD results from mutations in the DMD Gene, which produces a protein called Dystrophin. Dystrophin is critical for muscle stability and function. DMD patients suffer from lung infection, respiratory insufficiency, and cardiomyopathy. This leads to early deaths of the patients. With advancements in science, respiratory and cardiac support have extended the lifespan of patients, often by up to 30 years. The DMD gene spans 2.6 million base pairs and 79 exons. It is the largest protein-coding gene in the human genome. This makes it susceptible to deletion, duplication, and point mutations, which disrupt the reading frame of the DMD gene. This would lead to nonfunctional or truncated dystrophin protein, causing severe DMD symptoms because the protein cannot regenerate muscle. The absence of dystrophin leads to progressive degeneration of muscles. This large 427 kDa isoform of dystrophin is a cytoplasmic sarcolemmal protein that links the extracellular matrix (ECM) and cortical cytoskeleton [3]. Elevated dystrophin expression directly hinders the dystrophin-associated glycoprotein complex (DAPC), making the membrane unstable and the muscles susceptible to injury, which eventually will be replaced by fibroadipose tissue in the body. Dystrophin expression is highest in skeletal, cardiac, and smooth muscles. A small amount can be found around specific locations of the CNS. That being said, therapies to restore dystrophin expression are rigorously under research [4].

DMD is caused by mutations in the dystrophin gene, which prevents the synthesis (transcription followed by translation) of functional dystrophin protein. Dystrophin is critical for muscle functioning, which acts as a structural link between the cytoskeleton of muscle fibres and the ECM [5]. This connection is established through the dystrophin-glycoprotein complex (DGC), stabilising the sarcolemma (the muscle cell membrane) and protecting muscle fibres from damage during contraction. The absence of dystrophin results in progressive muscle weakening, as muscle cells become fragile and prone to repeated injury [6]. Over time, chronic damage leads to inflammation, fibrosis, and fatty tissue replacement, further impairing muscle function. The disease affects both skeletal and cardiac muscles, causing progressive loss of mobility, respiratory difficulties, and eventual heart failure, which is the primary cause of death in DMD patients.

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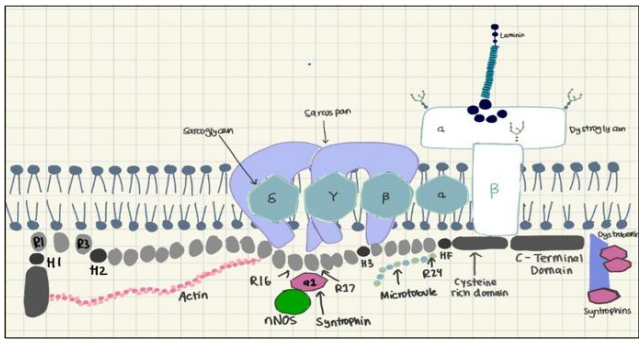



**[Fig.1: Dystrophin Protein [6]]**

Schematic representation of the dystrophin gene and its role in muscle fibre stability. The diagram highlights key domains of the dystrophin protein, its interaction with the sarcolemma, and the actin cytoskeleton.

Current trends in DMD treatments can be categorized into distinct niches, such as corticosteroids and physiotherapy. These only have palliative benefits, providing temporary treatments and not a cure for the disease altogether. Hence, the growing interest of researchers in gene intervention-based therapies is the only way to combat the disease. These approaches include, but are not limited to, utilizing AAV, CRISPR/Cas-9, and antisense oligonucleotides of the gene.

## II. GENE TRANSFER (AAV & MICRODYSTROPHIN)

The large size of the DMD gene poses challenges for gene therapy. Researchers have designed microdystrophin constructs to overcome this by removing non-essential regions while retaining their functional domains. These smaller constructs can be packaged into AAV vectors and delivered to muscle tissues [7]. The problem was addressed by the origination of micro-dystrophin genes (<4kb).

Around 30 different micro-genes have been scrutinised since 1997 [8]. Not all micro-genes have reduced the muscle disease; many have shown significant efficacy in various mouse models. A recent experiment performed with young adult affected dogs further demonstrates that the administration of a high-dose AAV micro-dystrophin vector through the circulation is safe and results in body-wide transduction in affected large mammals. These preclinical outcomes indicate a promising sign for evaluating systemic AAV micro-gene therapy in humans.

The whole domain of the dystrophin protein consists of four hinges, the N-terminal (NT) domain, a cysteine-rich domain, 24 spectrin-like repeats and the C-terminal domain. Out of the four hinges, 1 and 4 are placed before and after 24 repeats. Hinges 2 and 3 are positioned in the centre of the 24 spectrin repeats [9]. In-vivo data confirmed that microgenes that carry four or five repeats, with or without a centrally located hinge, can protect muscle. However, due to the unavailability of a head-to-head comparison, it remains unclear which configuration provides better security. Remarkably, one of the trials has used a four-repeat micro-gene, and the other two trials have checked for two different five-repeat micro-genes. Interestingly, the micro-gene lacks the central hinge used in one trial, whereas the other two trials have employed a central hinge in their microgenes. The outcome of these ongoing trials will help to elucidate our interpretation [10].

Preclinical studies in animal models have demonstrated significant improvements in muscle function and pathology. Other clinical trials by Sarepta Therapeutics, Pfizer, and others show encouraging results [11]. However, further optimization of dosage, immune suppression, and long-term safety remains a challenge.

While gene therapy holds tremendous potential, several challenges remain. One primary concern is the immune response triggered by AAV vectors or the newly introduced dystrophin, which can lead to the destruction of treated muscle cells. Additionally, AAV vectors may be lost over time due to muscle cell turnover, requiring repeated administrations because AAV vectors do not integrate into the host genome. Another limitation is gene delivery efficiency, as achieving body-wide distribution of dystrophin remains a technical hurdle, particularly for larger muscle groups. Addressing these challenges requires advancements in immune modulation strategies, more efficient gene delivery systems, and improved versions of micro-dystrophin that can provide long-term therapeutic effects [12].

The most chosen research messengers in gene therapy are Adeno-Associated Viruses (AAV). AAVs are selected as vectors in gene therapy and many other advanced therapies because they are non-pathogenic, and their replication can be easily controlled. AAVs belong to the parvovirus family group, and their genome consists of a single-stranded DNA molecule of around [13] 4.8 kilobases. AAVs depend on co-infection with other viruses, such as adenovirus, which assist in replication. This single-stranded genome consists of three genes known as Rep, involved in replication inside a host, Cap, involved in capsid formation of the virus, and the assembly (AAP), which increases transfection efficiency. These coding sequences are flanked by ITRs (inverted terminal repeats) that are needed for genome replication and packaging, serving as the origin of replication in the recombinant plasmid. The Rep gene encodes four proteins (Rep78, Rep68, Rep52, and Rep40), which are vital for viral genome replication, while the Cap gene expression gives rise to the viral capsid proteins (VP; VP1/VP2/VP3) that form an outer capsid shell to protect the viral genome. It is also actively involved in cell binding and endocytosis [14].

A milestone in the research was achieved when Samulski and colleagues developed a method for recombinant AAV (rAAV) construction utilising a system referred to as the two-plasmid system, where the final virus stock is devoid of wild-type AAV (wtAAV) [15]. Under this, DMD (our gene of interest) replaces the rep and cap genes on the wild-type virus genome. But the inverted terminal repeats (ITRs) are still needed in cis for packaging and replication of recombinant AAVs. Technically, the only sequence of wild-type origin is the ITRs that are present in rAAV. Externally, the rep, cap, and helper virus genes are provided. It should be noted that rAAVs do not undergo site-specific integration into the human chromosome AAVS1 locus, unlike the wtAAV, and the bulk of rAAV genomes in the transduced cells remains as extra-chromosomal episomes [16]. This is a

robust and approved method of recombinant AAV production by transfecting the plasmid into adherent human embryonic kidney 293 (HEK293) cells, where the transgene, located between the ITRs, is delivered in cis, and the helper, rep, and cap genes are delivered externally. An alternate version of this method is the use of suspension culture of the HEK293 cell line, which pushes for higher yield along with rapid increased production of rAAV required for clinical applications. The recombinant virus produced is purified either by gradient or column chromatography, and the purity of the recombinant virus varies depending on the type of method adopted, which can again affect the results of pre-clinical and clinical studies. Epidemiological studies have confirmed the presence of antibodies against AAV in 40–80% of the human population, suggesting previous exposure to some of the AAV serotypes, namely AAV1, AAV2, AAV3, AAV5, AAV6, AAV7, AAV8, and AAV9. It is challenging to precisely determine the tissue tropism of AAV serotypes due to variations between studies. Among species, variations occur in the presence of respective viral receptors on target cells due to the tropism of the viral capsids. A fact that is sometimes ignored during translational studies is the different expression of receptors within species, causing variations in the potency of different AAV capsids [17].

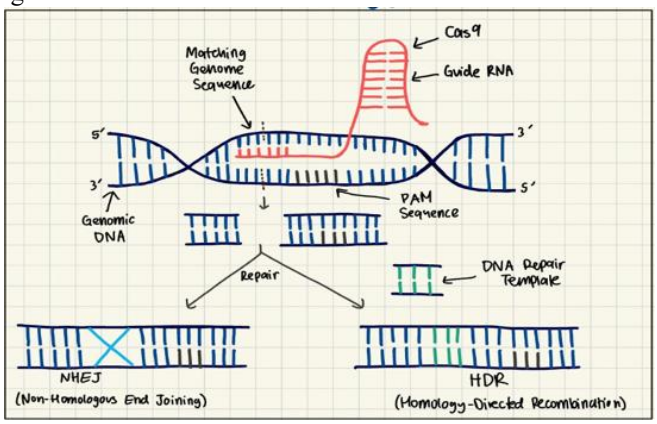
With the progress made with AAVs, in 2012, Glybera became the first approved gene therapy product for treating lipoprotein lipase deficiency. The next in line came out in 2017, by the FDA, named Luxturna, for the treatment of an inherited retinal disease, and one more FDA-approved gene therapy product was recognised in 2019, called Zolgensma, for treating spinal muscular atrophy [18].

## III. EXON SKIPPING

DMD is a disorder directly related to the loss of dystrophin expression caused by a mutation of the standard reading frame [19]. Exon skipping uses anti-sense oligonucleotides to bypass mutations in the DMD gene, which restores the reading frame by using the Anti-sense oligonucleotides (AOs). These short, single-stranded deoxynucleotides initiate the endonuclease-mediated knockdown by targeting the dystrophin pre-mRNA and subsequently inhibiting translation. This results in bringing the out-of-frame mutations into an in-frame one. By following this technique, functional dystrophin, though still internally defective, can convert into a milder version. With such specificity, exon skipping can benefit a larger group of DMD patients.

## IV. DETECTION

Duchenne muscular dystrophy (DMD) is diagnosed through a combination of clinical evaluation, laboratory tests, imaging, and genetic analysis [20]. Doctors first assess a child's developmental history and look for early signs, such as delayed walking, frequent falls, difficulty running, and a waddling gait, which typically become apparent between ages 2 and 5. A key clinical sign is Gowers' manoeuvre, where the child uses their hands to push against their legs to stand up due to proximal muscle weakness [21]. If DMD is suspected, a blood test measures creatine kinase levels, which are significantly elevated in DMD patients due to muscle breakdown and damage. Genetic testing is the definitive diagnostic tool for identifying mutations in the dystrophin gene that cause the disease. In cases where genetic results are inconclusive, a muscle biopsy may be performed to check for dystrophin protein levels using immunohistochemistry or Western blot analysis [22]. Electromyography (EMG) and cardiac evaluations, such as echocardiograms and electrocardiograms (ECGs), may also be used to assess muscle function and detect early signs of cardiomyopathy. Additionally, MRI scans can help visualize muscle degeneration.




**[Fig.2: CRISPR CAS9 Technology]**

Diagram illustrating CRISPR-Cas9 gene editing technology. The Cas9 enzyme, guided by a specific RNA sequence, introduces a double-strand break at the target DNA site, which is subsequently repaired by either non-homologous end joining (NHEJ)or homology-directed repair (HDR).

Early diagnosis is crucial for initiating treatment strategies, such as corticosteroids and physical therapy, to slow disease progression and improve quality of life. In some cases, prenatal testing can be performed for at-risk pregnancies, particularly when there is a known family history of DMD. This testing, usually done between 10 and 13 weeks of pregnancy, includes chorionic villus sampling (CVS) or amniocentesis, which are checked within 15 and 20 weeks. Both procedures analyse fetal DNA for mutations in the dystrophin gene. Noninvasive prenatal testing (NIPT), which examines cell-free fetal DNA in maternal blood, is also emerging as a potential early screening method for detecting X-linked conditions like DMD. Newborn screening for DMD has not yet been universally implemented, but pilot programs and research initiatives are exploring its feasibility. Some infant screening programs measure creatine kinase (CK) levels in dried blood spots from routine newborn screening panels, as elevated CK levels may indicate muscle damage consistent with DMD. If CK levels are high, genetic testing is conducted to confirm a dystrophin gene mutation. Early newborn screening can allow
for prompt interventions, genetic counselling, and potential enrollment in clinical trials to slow disease progression. Expanding newborn screening programs for DMD is an ongoing area of research and advocacy to improve early diagnosis and access to emerging therapies [23].

## V. GENE EDITING

A widely accepted gene editing tool, known to accurately act on gene mutations by utilising either a homology-directed repair (HDR) or non-homologous end joining (NHEJ) approach [24], is CRISPR/Cas9. This approach is derived from the bacterial immune system's response to viruses. CRISPR/Cas9 consists of a CRISPR-associated endonuclease (Cas) and a guide RNA (gRNA), which together form a Cas9-gRNA complex-ribonucleoprotein directed toward the faulty, targeted DNA. Once spotted, RNA-guided endonuclease Cas9 produces site-specific ds breaks, creating RNA–DNA heteroduplex followed by nucleic acid recognition [25]. With the ability to permanently edit specific genes, numerous experiments utilising CRISPR/Cas9 to alter DMD-causing mutations have been conducted in recent years. While delivery efficiency was not addressed, adapting the CRISPR /Cas9 approach remains a significant challenge.

## VI. CLINICAL TRIAL AND APPROVED THERAPY

An increasing number of pharmaceutical companies and biotech startups are showing interest in developing therapies for DMD. Despite these progresses, some challenges remain, with the significant problem of delivering the treatment to all the muscles in our body. Nevertheless, the cure is still elusive, but there has been a rapid growth in the number of treatments advancing to clinical trials that can potentially improve the quality of life among DMD patients. Regulatory agencies have approved some of these therapies in the USA, Japan, and Europe [26].

The clinical trial PF-06939926, currently ongoing in Pfizer's Phase 1b, is evaluating the safety, efficacy, and tolerability of a single IV administration of micro-dystrophin in ambulatory and non-ambulatory DMD patients through an AAV9-mediated transfer of micro-dystrophin. Preliminary data obtained from 5 of 6 boys showed few positive signs (or at least no deterioration) in the NorthStar Ambulatory Assessment (NSAA), compared to patients who received a placebo. Serious/Side effects were seen in a few patients. A tragic death was reported, putting the trial on hold [27].

An AAV9-mediated, SGT-001, microdystrophin gene transfer from Solid Biosciences is also under a phase I clinical trial, IGNITE DMD. Due to an adverse condition reported in one patient under trial, the trial was suspended. The study resumed recently with a revised clinical trial protocol for SGT-001, manufactured using second-generation protocols. An ongoing trial by Sarepta Therapeutics, Inc. is investigating the safety and efficiency of the IV administration of rAAVrh74.MHCK7 microdystrophin (SRP-9001), in a first open-label phase I/II trial (NCT03375164). 12-week data of dystrophin expression and a promising safety profile were reported from the first 11 patients. Unfortunately, preliminary data from the clinical trials have demonstrated a lack of success and missed efficacy milestones. To date, data from human trials have not reported significant success, as seen in animal studies, highlighting that these approaches require further enhancements [28].

Ataluren [29] (TranslarnaTM), developed by PTC, is a small molecule that is orally administered and designed to enable the formation of a functioning protein in patients carrying a genetic deformity due to a nonsense mutation. Ataluren showed successful efficacy in its in vivo mouse model. However, challenges in replicating this finding raised a question about the effectiveness of Ataluren against stop codons, supported by data showing functional improvement in cell models of Hurler syndrome and mouse models of nonsense mutation-associated cystic fibrosis. Ataluren made it to the clinical trials. In 2014, EMA granted conditional marketing authorization. A Phase IIb trial involving 174 randomised patients and a Phase III trial involving 230 randomised patients are ongoing. Ataluren was performing well in these trials. However, significant challenges were faced in achieving an improved walk in the 6-minute walk test from the 48-week primary endpoint compared to patients who received only a placebo. Still, an enhanced trend of efficacy was reported, with a 29-minute increase in SMWT and improved timed function tests in individuals who received Ataluren.

Compared with a placebo. Notably, less evidence supports the efficacy of Ataluren or the delivery of the drugs to the heart [30].

## VII. FUTURE PERSPECTIVE/CONCLUSION

DMD is indeed a complex, lethal disease. In DMD, successful treatment for heart/skeletal muscle weakness necessitates the development of a combinatorial approach to achieve desired outcomes. Additionally, genetic manipulations to correct the genetic defect and target the secondary effects caused by the lack of dystrophin should be the prime area of focus. Furthermore, DMD is also inherited through generations. The development of a proper treatment is critical, not only to prevent the defect but also to cure patients who are already affected. Various diagnoses are successfully in place to understand the stage of DMD and the changes happening inside the muscles at its onset. The primary concern now remains the therapies to cure this disease. Exploring the current options, gene therapy shows a promising future. AAV vectors have proven to be a stable, innovative mediator that can be used in the treatment. In recent decades, gene therapy has evolved from merely a conceptual phase to clinical trials for over 1400 rare disorders. If successful, the overall result of the trials and advancements in this field over time can completely reestablish modern medicine, eradicate diseases currently called ‘incurable’, and even give the human race a grasp over evolution.

## DECLARATION STATEMENT

After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

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- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Author's Contributions:** The authorship of this article is contributed equally to all participating individuals.

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## AUTHOR'S PROFILE

**Anoushka Dhawan** is a high school senior at Livingston High School in New Jersey, USA. With a strong academic background and a weighted GPA of 4.13, she has pursued a rigorous curriculum that includes AP Physics, AP Chemistry, AP Precalculus, and Intermediate Science Research Methods. Her academic strengths are reflected in her ACT super score of 35 and a score of 5 on the AP Human Geography, Precalculus and English Language exams. Anoushka's research interests lie in oncology, molecular biology, and regenerative medicine. She has been actively involved in scientific research through her school's three-year science research program and an intensive summer internship at the Gerhardt Lab at Weill Cornell Medicine. At Cornell, she contributed over 50 in-lab hours, assisting with DNA Fibre Assays and immunofluorescence imaging to study replication mutations in BRCA1 cell lines under various treatments. At school, she proposed a project focused on using iPSC-derived organoids to study the progression of ovarian cancer, which she presented at her school's annual science symposium. In addition to research, Anoushka demonstrates leadership through advocacy and outreach. She authored and illustrated Friendships Without Boundaries, a children's book to raise awareness for Duchenne Muscular Dystrophy (DMD), which six elementary schools in her district have adopted. She also played a pivotal role in initiating a township proclamation for Duchenne Awareness Day and raised over $3,000 through a charity marathon. Anoushka is fluent in English, Hindi, Bengali, and Spanish. She is a nationally ranked varsity tennis player and serves as a private and assistant coach for middle school students. Her work as a social media manager for the nonprofit HealDMD and as treasurer for the Shanti Bhavan Education Alliance reflects her dedication to social change through education and science.

**Sulagna Dutta** is a Senior Research Scientist working with Syngene International, Bangalore, India. She holds a Master of Science in Biotechnology. She has around 8 years of experience in Bioassays, in vitro assays, and immunogenicity. She has working experience in gene and Cell Therapy, Antibody-Drug conjugates, monoclonal antibodies, and vaccines. Her love for research drove her to help students who are keen to join research soon.