Review

The Multi-System Roles of Dp71 Dystrophin Isoforms in Duchenne Muscular Dystrophy

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Review

The Multi-System Roles of Dp71 Dystrophin Isoforms in Duchenne Muscular Dystrophy

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Abstract

The *DMD* gene is well known for its product dystrophin, a large rod-shaped protein that plays a critical role in muscular membrane strength and integrity. Mutations affecting dystrophin lead to Duchenne muscular dystrophy, a fatal X-linked disease characterized by muscular weakness and breakdown. In addition to the full-length dystrophin product that is most often associated with disease, the *DMD* gene also encodes for multiple shorter isoforms of dystrophin with diverse functions. One isoform in particular, Dp71, has been increasingly found to play a wide variety of roles throughout the body. In this review, we consolidate the numerous studies on Dp71 to provide a comprehensive foundation for future work. We outline and summarize the current state of knowledge on the role of Dp71 in the brain, the retina, and skeletal muscles. We also explore Dp71-based therapies currently being tested in the pre-clinical landscape.

Keywords: dystrophin; Dp71; Duchenne Muscular Dystrophy; isoform

1. Background

Duchenne muscular dystrophy (DMD) is a debilitating X-linked recessive neuromuscular disorder characterized by progressive degeneration of skeletal muscles [1,2]. Cognitive and neuropsychiatric comorbidities are also prevalent [3]. DMD has a presumed global incidence of around 1 in 3,500 to 5,000 live male births, with symptoms usually manifesting in early childhood, most often between ages of 2 and 3 years [4,5]. Loss of independent ambulation typically occurs by 10 to 12 years of age [4,6]. Clinical interventions have improved the natural history of DMD, yet the condition remains life-threatening due to progressive cardiac and respiratory complications, and life expectancy extends into the third or fourth decade [4,6]. The underlying cause of DMD is a mutation in the *DMD* gene located at Xp21.1, which measures approximately 2.4 million base pairs and encodes a protein of 3,685 amino acids, making it the largest gene found in the human genome [7,8]. Most pathogenic mutations encompass large deletions or duplications that disrupt the open reading frame, thereby preventing the synthesis of functional dystrophin protein [9,10].

Dystrophin acts as a mechanical link between the intracellular F-actin cytoskeleton and the extracellular matrix through association with the dystrophin-associated glycoprotein complex (DAPC) at the sarcolemma [11,12]. This linkage is fundamental for proper muscle fiber contraction, and its absence leads to sarcolemmal fragility, chronic inflammation, repeated myofiber degeneration, and inability to regenerate [13].

The primary product of the *DMD* gene in skeletal and cardiac muscle is the full-length dystrophin protein, Dp427m [14]. Beyond the 79 exons that collectively encode the full-length dystrophin protein, the locus exhibits considerable genetic complexity, producing multiple tissue-specific isoforms through alternative promoters and differential splicing [2,3]. This genetic flexibility results in several shorter C-terminal variants, including Dp260, Dp140, Dp116, and Dp71 [2,15]. Among these, Dp71 is the second smallest but the most ubiquitously expressed isoform, serving as the predominant dystrophin product in non-muscle tissues such as the brain, kidney, liver, lung, and

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testis [16]. While traditionally described as absent from skeletal muscle, recent studies have confirmed the presence of both Dp71 transcript and protein in skeletal muscle tissue [17].

Before the early 1990s, investigations of dystrophin primarily addressed the full-length protein encoded by a 14 kb mRNA, until subsequent identification of distal DMD transcripts revealed shorter isoforms, such as Dp71 [16,18,19].These studies identified a previously unrecognized transcript initially reported as 6.5 kb, encoding a smaller dystrophin-related protein distinct from full-length dystrophin in both structure and tissue distribution, which was later clarified to be 4.8 kb in length [3,16,18,20].

At the protein level, Dp71 is a 70–75 kDa dystrophin isoform derived from an internal promoter located within intron 62 of the DMD gene [18–22]. Dp71, unlike the complete dystrophin protein, lacks the N-terminal actin-binding domain but retains the cysteine-rich and C-terminal regions, which anchor the protein to the DAPC [3]. Formerly known as apodystrophin-1, Dp71 exhibits functional diversity due to alternative splicing of exons 71–74 and 78, which results in different variants with distinct C-terminal sequences and expression patterns [2,23,24]. As a result, the DMD gene displays sophisticated organization and regulation by producing structurally unique proteins through independent internal promoters. Fourteen distinct Dp71 splice isoforms have been catalogued to date (Figure 1) [3].

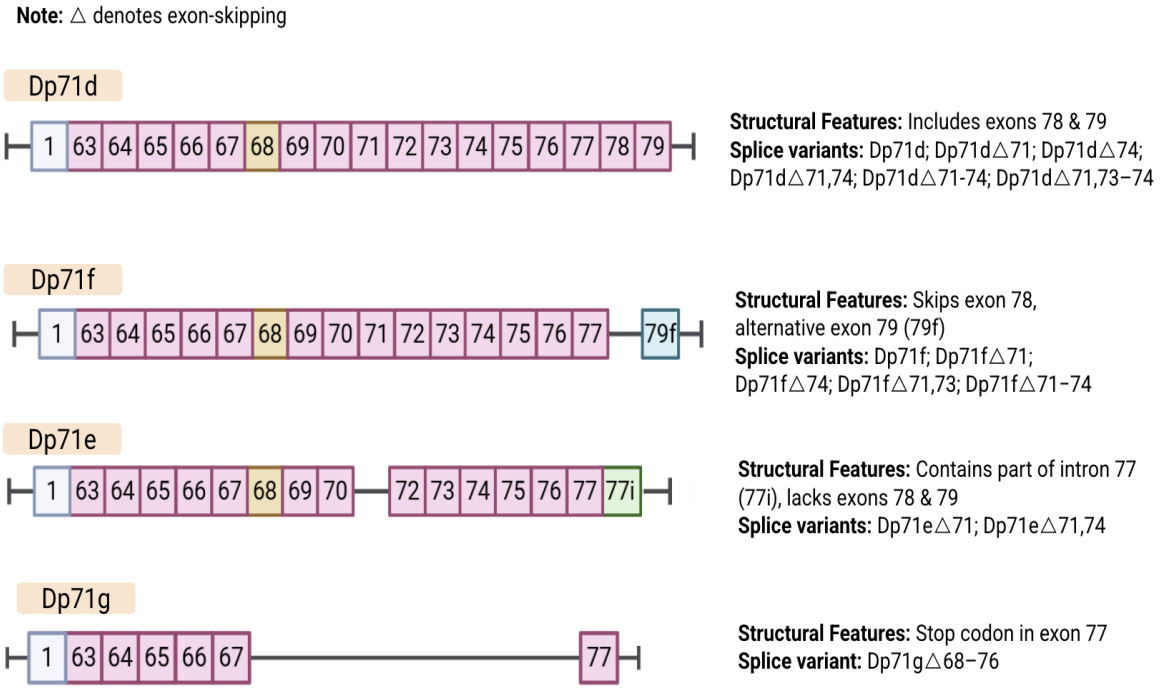

Figure 1. Structural Characterization of Dp71 Splicing Variants. The Dp71 isoform exhibits C-terminal diversity, with alternative splicing generating distinct variants. Exon organization of the major variants (D–G) are presented.

As a key product of the DMD gene, Dp71 has an important role in the brain and other tissues, and is implicated in the non-muscle manifestations linked to DMD [22,25]. Research using Dp71 reporter mice has confirmed its presence in the adult central nervous system, retina, and kidney epithelium, hinting at roles in neural function, vision, and epithelial–basal lamina interactions [26]. Beyond its structural contributions, Dp71 is actively involved in a range of cellular activities, including neural development, the organization of synapses, the regulation of water balance, and DNA repair mechanisms, all of which are essential for maintaining cellular stability and signaling across tissues [3,15]. Dp71 functions through DAPCs in several subcellular compartments, such as the plasma membrane and nucleus, to support cell organization and homeostasis. Disruption of Dp71

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expression due to mutations in the distal DMD gene is strongly associated with cognitive impairment and other non-muscle features related to DMD, with neurological severity increasing with the loss of shorter isoforms, including Dp71 and Dp140 [3]. This review integrates current knowledge regarding Dp71, with a focus on its roles in neurological, retinal, and muscular systems, and evaluates emerging therapeutic approaches. A brief visual summary of systems affected by Dp71 is presented in Figure 2 (Figure 2).

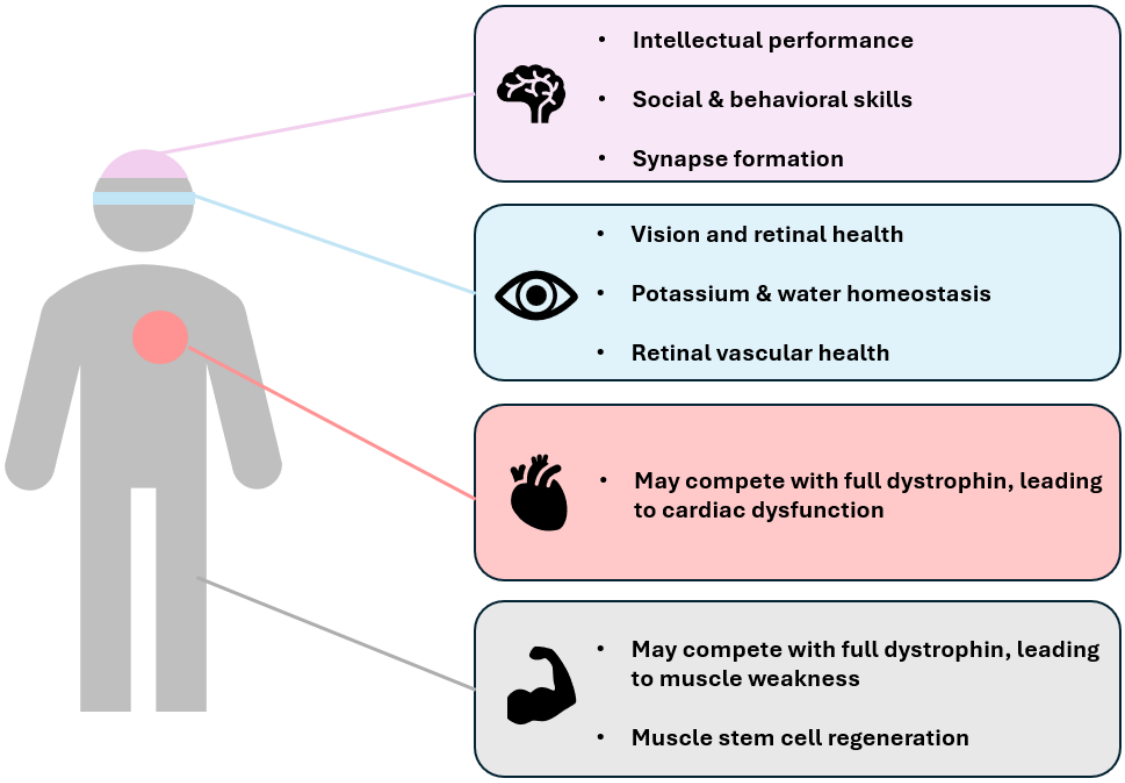

Figure 2. A Visual Guide to the Roles of Dp71. Dp71 has diverse roles throughout the body. While primarily known for its effects on the brain and retina, Dp71 has been shown to compete with full-length dystrophin and lead to dysfunction in skeletal and heart muscle.

2. Neurological and Behavioral Roles of Dp71

The primary role of Dp71 pertains to its impact on neurological health and function, and numerous studies have explored the neurological roles of Dp71 in both the clinical and pre-clinical setting. Dp71 is essential for brain maturation, and its expression varies from embryogenesis to adulthood. As the main dystrophin isoform in the adult brain, Dp71 expression varies across tissues, including glial cells, retinal neurons, and kidney epithelia [27–29]. In the human embryonic brain, Dp71 is notably active at important stages of growth in the cortex and hippocampus, implying that it is engaged in early brain developmental processes vital for memory and cognition [30]. An expression profile during the human brain development process shows that Dp71 is present in different brain regions and retains expression throughout life, even though levels are lower in the cerebellum [30]. In studies using embryonic rodent brain tissues, it was demonstrated that Dp71 isoforms change over time: Dp71f dominates during embryogenesis, particularly during the expansion of neural stem cells and the formation of glial cells, while Dp71d becomes the primary isoform postnatally [31,32].

Protein interaction investigations in embryonic mouse neural progenitor cells have identified dystroglycan, dystrobrevins, and syntrophins as principal components of macromolecular complexes associated with Dp71 in the developing forebrain [31]. The composition and stability of these

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complexes are dependent on developmental stage and cell type, indicating that Dp71 fulfills distinct functions during brain maturation. In mouse models, Dp71 is detected in Nestin-positive neural stem and progenitor cells, as well as in radial glia, which provide structural and signaling support during early corticogenesis [31]. Interestingly, while Dp71 expression appears to decline in developing neurons during differentiation, it resurfaces in mature neurons, where it localizes to inhibitory postsynaptic sites. These sites are defined by the presence of gephyrin, a specialized structural protein that anchors inhibitory receptors to the neuron's membrane [31]. In addition to its action at the synapse, Dp71 also forms DAPCs within the nuclei of hippocampal neurons [33]. Within the nucleus, it resides in nuclear speckles, which regulate gene expression, as well as in the nucleoskeleton, indicating that it is involved in transcription and RNA processing [33]. Collectively, these observations emphasize how Dp71 evolves from important roles within progenitor and glial biology to more specialized tasks in organizing mature neural circuits and forming DAPCs at inhibitory synapses.

Roles in Synaptic Organization and Molecular Compartmentalization

Beyond development, Dp71 fulfills a crucial role as a structural organizer for molecular machinery at synapses, which are essential for neuronal communication. In excitatory synapses, Dp71 organizes key postsynaptic proteins, including PSD-95, a major scaffolding protein that anchors glutamate receptors and other signaling molecules to maintain synaptic stability [34]. When Dp71 is absent, as seen in Dp71-null mice, the DAPC is compromised, producing difficulties in long-term potentiation (LTP), the process by which synapses strengthen over time to support memory formation, and a decrease in associated proteins, such as β-dystroglycan and α-syntrophin [35]. Further examination of these Dp71-null mice at the ultrastructural level reveals abnormalities in presynaptic vesicle positioning, including the displacement of presynaptic vesicles away from the active zone, the enlargement of vesicles in the distal pool, and the widening of synaptic clefts [36]. These structural alterations impair the effectiveness of neurotransmitter release, which corresponds to observed problems in synaptic plasticity, along with the overall stability of neural networks [36].

Recent in vivo compartment-specific studies using an HA-tag knock-in mouse model, in which Dp71 is labeled with a small tag for exact visualization, have allowed for a more comprehensive observation of its location [37]. In dentate granule neurons, Dp71 is found specifically at inhibitory synapses and glial endfeet, but not at the excitatory synapses of CA1 pyramidal neurons [37]. This localization pattern suggests that Dp71 is mainly involved with glial and inhibitory synaptic areas. In these mice, Dp71 creates unique glycoprotein complexes at inhibitory postsynapses in dentate granule neurons and at glial endfeet near the blood-brain barrier [37]. These complexes interact with dystrobrevin-β, dystroglycan, and Insyn1 to preserve the structural stability of inhibitory synaptic frameworks. The molecular makeup of these Dp71 complexes is different from those formed by Dp427, showing that Dp71 forms specific complexes in particular synaptic locations. Furthermore, dystroglycan plays an integral role at the molecular level by anchoring the DAPC to the cell membrane, with Dp71 acting as the specific binding partner [37,38]. Experimental knockdown studies reveal that dystroglycan is strictly required for the proper submembranous localization and stabilization of Dp71, as its loss results in Dp71 dispersing throughout the cytoplasm, and the amount of Dp71 associated with the membrane decreases [38]. Furthermore, dystroglycan's interaction with Dp71 facilitates the phosphorylation of Dp71, suggesting that this partnership influences both where Dp71 is located and how it is modified after translation [31]. When this binding is broken, Dp71's positioning becomes unstable, and its phosphorylation pattern changes, potentially obstructing the proper organization of synapses. Given that dystroglycan complexes mediate membrane-cytoskeleton coupling and extracellular matrix signalling, the absence of Dp71 can give rise to structural instability in both synaptic and glial compartments [31].

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Excitation-Inhibition Imbalance in Cortical and Cerebellar Circuits

Dp71 is indispensable for maintaining the brain's electrochemical balance by regulating the interchange between excitatory and inhibitory synaptic transmission. In the medial prefrontal cortex (mPFC), Dp71-null mice manifest enhanced AMPA receptor-mediated excitatory transmission while inhibitory inputs remain intact, leading to an excitation–inhibition (E/I) imbalance [39]. These changes at the synaptic level are linked to issues with spatial working memory and a decline in executive flexibility, which suggests that the coordination of prefrontal networks is compromised [39]. In cerebellar circuits of Dp71-null mice, the lack of Dp71 ramps up excitatory transmission at the synapses between climbing fibers and Purkinje cells, as shown by larger excitatory postsynaptic currents compared to wild-type controls (about 2.0 nA versus 1.35 nA) [40]. Additionally, the ability of synapses to strengthen or weaken over time, known as activity-dependent synaptic plasticity, is disrupted in the absence of Dp71. In wild-type mice, cerebellar synapses strengthen with spikelet amplitudes, miniature electrical signals that reflect how easily a neuron can be triggered, rising to approximately 126% of baseline [40]. Contrarily, Dp71-null mice show no significant change in spikelet amplitude, sticking to baseline levels of around 100%, which indicates a failure of normal synaptic potentiation [40].

These circuit-level abnormalities translate into behavioral challenges in tasks that rely on the cerebellum. Dp71-null mice showcase slower learning and use less efficient strategies when navigating hidden-platform tests, even though their motor strength and coordination remain normal [40].

At the molecular level, the absence of postsynaptic Dp71 complexes leads to the destabilization of GABAergic scaffolds, the systems that hold inhibitory receptors in place, disrupting excitatory-inhibitory (E/I) balance across both hippocampal and cortical circuits [37].

Calcium Homeostasis

Maintaining proper calcium levels within cells is vital for healthy neurons, and Dp71 appears to play an important role in supporting the protein machinery that controls these levels. A study involving neurons derived from stem cells of a DMD patient with intellectual disabilities revealed that when Dp71 is diminished or mislocalized, it interferes with the proper assembly of the DAPC and its interaction with SERCA2, a calcium pump in the endoplasmic reticulum (ER) responsible for removing surplus calcium from within the cell [41,42]. In cases where Dp71 is absent, neurons exhibit elevated resting calcium levels in their cytoplasm and attempt to compensate by raising SERCA2 expression, denoting a possible link between Dp71 loss and heightened neuronal sensitivity that underpins cognitive impairments [41,42]. Interestingly, even with a rise in SERCA2 expression, the ER still struggles to release calcium effectively, leading to a continual calcium imbalance and poor calcium transmission. Ultimately, these studies demonstrate that a deficiency in Dp71 directly disrupts intracellular calcium homeostasis in neurons [41].

Calcium homeostasis is critical for synaptic plasticity, neural excitability, and gene transcription, and disruptions of intracellular calcium have been associated with impaired learning and memory [41,42]. Consequently, the loss or misplacement of Dp71, along with its related DAPC, further compromises membrane protein structures and likely contributes to the observed calcium-mediated signaling issues in mice [34].

Astrocytic and Perivascular Roles of Dp71

Dp71 is an important constituent of the blood–brain barrier and is predominantly localized at the perivascular endfeet of astrocytes [43]. In this location, it has a central role in organizing the DAPC and verifying the correct placement of aquaporin-4 (AQP4) water channels and Kir4.1 potassium channels [43]. The aforementioned structural arrangement is necessary for maintaining water and potassium homeostasis, supporting the connection between neural activity and blood flow (neurovascular coupling), and controlling neuron excitability. Therefore, if Dp71 is absent, it could

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upset these regulatory functions, conceivably increasing neural excitability. Studies in mice have indicated that during ischemic injury, Dp71 undergoes breakdown through a process known as ubiquitin-mediated degradation [43]. This degradation leads to the misplacement of AQP-4 channels, which are necessary for water transport, within the astrocytic endfeet surrounding blood vessels. Consequently, this misplacement contributes to the buildup of interstitial fluid in the brain tissue, worsening swelling referred to as vasogenic edema [43].

Social and Behavioral Abnormalities in Mice

Investigating mouse models lacking Dp71 has shed insight into the critical roles of various dystrophin isoforms in motor control, cognitive function, and emotional regulation. For instance, mdx3cv mice with a deficiency in both the full-length Dp427 and shorter isoforms, including Dp260, Dp140, Dp116, and Dp71, exhibit a slight delay in operant learning, but overall task acquisition and retention are comparable to wild-type controls [44]. Similarly, their performance in short-term and working memory tests, such as the T-maze, is largely unaffected. In contrast, mdx mice, which lack full-length dystrophin but retain Dp71, do not show significant differences from control groups in operant and T-maze assessments [44]. Notably, mdx3cv mice present amplified anxiety and more pronounced stress reactions in light-dark tests [44]. While the absence of multiple isoforms in mdx3cv mice complicates crediting these behavioral patterns solely to Dp71, a comparison with mdx mice reveals that the loss of C-terminal isoforms, including Dp71, can aggravate learning difficulties and anxiety-related behaviors. Furthermore, Dp-71 null mouse models display specific impairments in navigation activities reliant on the cerebellum [40]. These mice have slower acquisition and employ less efficient search strategies in hidden-platform spatial tests, despite maintaining normal motor strength, coordination, and general movement [40].

Dp71-null mice also display specific changes in their social and emotional behaviors [45]. While their overall sociability appears normal, these mice show less interest in social novelty, which could suggest difficulties recognizing social cues or simply a lack of curiosity about new peers. Their socially driven ultrasonic vocalizations are also impacted, with longer calls and a noticeable change in the types of calls they make, leaning more towards peak, sinusoidal, and U-shaped patterns [45]. This points to a disturbance in their social communication. When it comes to emotional responses, Dp71-null mice demonstrate a moderate increase in anxiety-like responses, such as increased thigmotaxis in open-field tests and altered risk assessment in elevated plus-maze and light–dark paradigms [45]. These behavioral changes occur without any evident motor issues, myopathy, or fear-related memory and learning deficits. The observed behavioral profile in Dp71-null mice parallels the descriptions of autistic characteristics and executive function challenges in individuals with distal DMD mutations [46].

Dp71 Disruption and Severe Intellectual Disability

The level of cognitive impairment in DMD is determined by the location of the mutation within the dystrophin gene, with mutations that disrupt the brain-expressed Dp71 isoform acknowledged as a significant predictor of severe intellectual disability [46,47]. Early clinical studies discovered that mutations in the distal C-terminal region are overrepresented in patients with cognitive impairments, underscoring the role of Dp71 and other short isoforms in neurocognitive function [48,49]. The discovery of a three-base pair deletion in Dp71 that results in intellectual impairment without muscular dystrophy substantiates this relationship [50]. Large cohort studies illustrate that individuals with mutations predicted to eliminate Dp71 expression have considerably lower Full-Scale Intelligence Quotient (FSIQ) scores than people with mutations that spare Dp71 [47]. On average, Dp71 deficiency reduces IQ by about two standard deviations, and most affected individuals meet criteria for severe intellectual disability, defined as an IQ below 50 [47,51,52]. Recent multicenter studies provide additional stratification: 64% of patients with mutations downstream of exon 63 that disrupt Dp71 had intellectual disability [46]. This incidence is much greater than the 25% reported in individuals with mutations affecting Dp260, Dp140, or Dp116, and the 15% in those with mutations

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limited to the long Dp427 isoform. Collectively, these findings highlight the loss of Dp71 as the primary driver of severe cognitive impairment in DMD.

Dp71-Specific Neurophysiological and Behavioural Impairments

Disruption of Dp71 caused by distal mutations results in numerous cognitive and behavioral impairments. Neuropsychological tests illustrate that boys with distal mutations affecting Dp71 had severe impairments in working memory, verbal reasoning, and reading acquisition, as well as reductions in verbal IQ (VIQ), performance IQ (PIQ), and FSIQ scores [51,52]. Behavioral assessments additionally reveal that Dp71 disruption contributes to poor social and emotional functioning [46]. Elevated scores on the Social Communication Disorder Checklist (SCDC) are observed in DMD patients, with the most pronounced deficits in individuals lacking short brain dystrophin isoforms including Dp71. These mutations are also associated with the lowest IQ scores and the most pronounced working memory deficits within the studied population [46]. Furthermore, the loss of Dp140 and Dp71 is associated with increased rates of neuropsychiatric comorbidities, including attention-deficit/hyperactivity disorder (ADHD), autistic features, and broader executive dysfunction [46,53]. In DMD patients without intellectual disability, distal mutations affecting Dp71 are linked to subtle impairments in specific cognitive domains, such as implicit learning, which may be attributable to dysfunction in cerebro-cerebellar circuits [54]. More pronounced cognitive deficits are generally observed in DMD patients with intellectual disability [54]. Overall, these clinical findings show that Dp71 loss is associated not only with intellectual disability, but also with executive and social-behavioral dysfunction.

3. Dp71 in the Retina

Regulation of Müller Cell Homeostasis

Although Dp260 is generally regarded as the primary dystrophin isoform in the retina, Dp71 has also been found to be involved retinal development and function. Dp71 expression in the retina was originally explored following the observation that mice with N-terminal *DMD* mutations displayed more severe electroretinogram (ERG) defects than mice with C-terminal *DMD* mutations, suggesting the involvement of short dystrophin isoforms [55]. Dp71 was found to localize to the inner limiting membrane (ILM) and blood vessels of the retina, whereas Dp260 localizes to the outer plexiform layer, indicating distinct expression patterns and roles. Dp71 in the ILM was further found to co-localize with dystrophin-associated protein complex (DAPC) in Müller cells, the retina-specific glial cells that are critical for retinal structure and stability [56–58]. Dp71 is ubiquitously expressed in all retinal precursors during early embryonic development but becomes layer-specific as the retinal cells differentiate [59].

The primary mechanism of Dp71 in the retina is to regulate the membrane transport of potassium and water, which has direct effects on Müller cell homeostasis and vascular permeability [60]. Dp71 forms a unique DAPC in Müller cells, and this complex is important for the appropriate anchoring and localization of both inwardly rectifying potassium channels (Kir4.1) as well as the neuronal aquaporin, AQP4 [61]. Thus, Müller cells isolated from Dp71-deficient retinas show impaired potassium conductance [61,62]. Similarly, in mouse models lacking Dp71, the localization and overall expression of Kir4.1 is impaired, while for AQP4 localization is impaired but overall expression is not affected [61,63,64]. Interestingly, experimental detachment of the retina in mice has also been shown to reduce the expression of both Kir4.1 and Dp71 in isolated Müller cells, suggesting the possibility of bi-directional regulation between Dp71 expression and retinal health [65]. Beyond AQP4 and Kir4.1, Dp71 deficiency has also been associated with elevated vascular permeability of the blood retina barrier (BRB), as well as impaired retinal vascular development in young mice [65,66]. Mice with a Dp71 deletion have been shown to experience elevated retinal vascular inflammation, vascular lesions, and capillary degeneration, suggesting a possible contribution to retinal vascular disease as well [67].

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Electroretinographic Abnormalities

Electroretinographic studies in Dp71-deficient mice have also established the importance of Dp71 for retinal function. The *mdx3cv* model, which lacks all dystrophin isoforms, was originally demonstrated to show abnormal ERG findings similar to that observed DMD patients, characterized by reduced b-wave amplitudes [68]. Of note, the lack of all dystrophin isoforms in this model makes it difficult to ascertain whether any change is due to the absence of Dp71, or some other isoform. More recently, studies in Dp71-null mice have explicitly confirmed that this reduction in ERG B-wave amplitude is due to the loss of Dp71, rather than Dp260 [69]. Lastly, Dp71-null mice have been found to show elevated rates of cataract formation, although this is not typically something observed in DMD [70].

Clinically, only a single study has explored the contribution of Dp71 to vision defects in patients. Ricotti et al. stratified ocular abnormalities by *DMD* mutation location, and found that patients with mutations affecting Dp71 expression showed the most pronounced ERG defects [71]. Specifically, these patients showed a highly electronegative scotopic ERG, even compared to patients lacking Dp260. Given the number of pre-clinical studies that have identified the importance of Dp71 in the retina, future clinical studies should continue to expand upon the findings of Ricotti et al. to better characterize clinical manifestations of Dp71 deficiency on retinal function.

4. Dp71 in Cardiac and Skeletal Muscle

Compared to the studies on neuronal and retinal expression, the contributions of Dp71 to skeletal muscle are relatively understudied, and occasionally conflict with one another. Dp71 was not originally thought to be expressed in skeletal muscles, but recent publications have refuted this claim and identified both Dp71 transcript and protein in human skeletal muscle [17,72]. Dp71 expression has also been confirmed in myogenic cell culture from fetal muscle origin [73].

Dp71 Transgene Expression Exerts a Dominant Negative Effect

Several studies have found that Dp71 expression in the muscle may exert a detrimental effect. It was originally reported that although transgenic Dp71 can effectively colocalize with the DAPC in muscle tissue, muscle pathology remained severely dystrophic, suggesting minimal function in the Dp71-bound DAPC. [74]. It was later theorized that skeletal muscle expression of Dp71 may exert a dominant negative effect by competing with full length dystrophin for DAPC binding sites [75]. Transgenic overexpression of Dp71 in healthy mice led to muscle damage similar to a dystrophic mouse, marked by muscle fiber degeneration and elevated serum creatine kinase [75]. Although there was no change in isometric tension between healthy and transgenic animals, Dp71-overexpressing mice were found to have a higher risk of sarcolemmal rupture [76]. Most recently, it was observed that healthy mice with transgenic overexpression of human Dp71 demonstrated normal skeletal muscle function, but impaired cardiac muscle function reminiscent of a dilated cardiomyopathy [77]. Transgenic mice displayed reduced ventricular ejection fraction and reduced ventricular wall thickness as early as 3 months of age, and by 12 months transgenic mice showed elevated systolic volumes and reduced ejection fraction relative to healthy controls [77].

Functional testing in *mdx52* mice, which only express Dp71, and DMD-Null mice, which express no isoforms, revealed no change in grip strength or treadmill performance between the two models, further suggesting a low contribution of Dp71 to these parameters [78]. Interestingly, Dp71 expression – specifically Dp71ab - has been identified in muscle precursor satellite cells, and Dp71ab overexpression was associated with enhanced myoblast proliferation in vitro [79]. These findings suggest that Dp71 may have roles in muscle that do not involve association with the DAPC, and should be explored further.

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Clinical Evidence for the Role of Dp71 in Muscle is Mixed

Clinical data regarding the importance of Dp71 to skeletal muscle function is mixed. Analysis of patient motor outcomes in a clinical trial setting identified that patients with *DMD* mutations affecting Dp71 expression showed significantly worse performance in the time-to-stand test compared to *DMD* mutations that do not alter Dp71 [80]. However, no other test parameters in this cohort showed a change in severity based on mutation type. A separate study also found that North Star Ambulatory Assessment (NSAA), a measure of motor ability, is significantly reduced in patients with Dp71-affecting *DMD* mutations compared to DMD patients with preserved Dp71 expression [78]. In contrast, genotype-phenotype correlations from a Canadian DMD registry found that patients with Dp71-affecting mutations were significantly less likely to require wheelchair use than other DMD patients [81]. These discrepant results warrant further clinical and pre-clinical studies to better understand the contribution of Dp71 to skeletal muscle function and clinical severity.

5. Emerging Dp71-Based Therapies

While no Dp71-specific therapies have yet been translated into clinical trials, several studies have explored the preclinical therapeutic utility of Dp71 overexpression. Given the retinal and cognitive deficits observed due to the lack of Dp71 expression, it was theorized that Adeno-associated virus (AAV)-mediated delivery of a Dp71 transgene may serve as an effective therapy to treat these symptoms. Uptake of AAV into Müller cells is typically very low, so early studies focused on the development and optimization of AAV serovariants that displayed elevated Müller cell uptake [82]. Using directed evolution, a variant called AAV ShH10 was identified that showed effective and selective uptake into Müller cells following intravitreal injection [82]. Interestingly, AAV-ShH10 showed higher transduction efficiency in the Müller cells of Dp-71 deficient mice compared to healthy mice, possibly due to membrane damage [83].

Dp71-Null mice treated via intraretinal injection with Dp71 transgene packaged in AAV-ShH10 showed significant expression of Dp71 transcript and protein that was specific to Müller cells, with higher expression than both untreated Dp71-Null mice and WT mice [84]. This overexpression was associated with significantly elevated AQP4 and Kir4.1 expression in treated mice, and the restored localization of these proteins to Müller cell endfeet. Permeability of the BRB was also restored to WT levels in treated mice [84]. A follow-up study later identified that this treatment was associated with improved ERG performance [85]. Dp71-Null mice generally show impairment on ERG characterized by reduced b-waves and smaller response amplitudes. Compared to sham-treated controls, Dp71-Null mice treated with intraretinal ShH10-Dp71 showed a fully recovered ERG response consistent with healthy mice [85]. These findings show that Dp71-based therapies, specifically viral transgene delivery, may be an effective tool for addressing vision defects in patients with Dp71 deficiency.

Most recently, the Dp71 transgene was packaged in an AAV9 vector and delivered to neonatal Dp71-Null mice through intracardiac injection, which led to significantly elevated Dp71 expression in the hippocampus, cerebral cortex, and cerebellum [86]. However, treatment failed to show any benefit in behavioral or anxiety-like symptoms measured through light-dark choice testing, elevated maze testing, or open field testing. Together, these data suggest that Dp71 overexpression may have therapeutic value for the retinal defects of DMD, but not for the cognitive defects. Given the established dominant negative effects that may arise with systemic treatment and transgene expression of Dp71 in muscle, any putative therapy should take care to assess safety risks in muscle tissue. Prior studies did identify that the BRB in Dp71-Null mice remains impermeable to ShH10-GFP despite the known BRB damage in this model, suggesting that intravitreal injection will not lead to systemic transgene expression, however this must be validated in humans as well prior to any translation [82].

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6. Conclusions

Dp71 has been shown to play a steadily increasing number of diverse roles throughout the body. It is critical for neuronal development and synaptic function, and the absence of Dp71 is associated with both cognitive and behavioral deficits. It also plays a key role in retinal health and function, and the loss of Dp71 is a contributing factor to impaired vision and retinal vascular health. Finally, Dp71 is implicated in a growing number of interactions with skeletal muscle, and the data is mixed on whether the presence of Dp71 in muscle is a net benefit or a detriment to muscle strength and function. The full scope of system-wide Dp71 interactions should continue to be explored in future studies, particularly as some therapies explore the possibility of Dp71 transgene expression.

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