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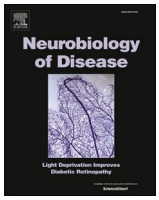

Synaptic alterations as a neurodevelopmental trait of Duchenne muscular dystrophy

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ABSTRACT

Dystrophinopaties, e.g., Duchenne muscular dystrophy (DMD), Becker muscular dystrophy and X-linked dilated cardiomyopathy are inherited neuromuscular diseases, characterized by progressive muscular degeneration, which however associate with a significant impact on general system physiology. The more severe is the pathology and its diversified manifestations, the heavier are its effects on organs, systems, and tissues other than muscles (skeletal, cardiac and smooth muscles). All dystrophinopaties are characterized by mutations in a single gene located on the X chromosome encoding dystrophin (Dp427) and its shorter isoforms, but DMD is the most devasting: muscular degenerations manifests within the first 4 years of life, progressively affecting motility and other muscular functions, and leads to a fatal outcome between the 20s and 40s. To date, after years of studies on both DMD patients and animal models of the disease, it has been clearly demonstrated that a significant percentage of DMD patients are also afflicted by cognitive, neurological, and autonomic disorders, of varying degree of severity. The anatomical correlates underlying neural functional damages are established during embryonic development and the early stages of postnatal life, when brain circuits, sensory and motor connections are still maturing. The impact of the absence of Dp427 on the development, differentiation, and consolidation of specific cerebral circuits (hippocampus, cerebellum, prefrontal cortex, amygdala) is significant, and amplified by the frequent lack of one or more of its lower molecular mass isoforms. The most relevant aspect, which characterizes DMD-associated neurological disorders, is based on morpho-functional alterations of selective synaptic connections within the affected brain areas. This pathological feature correlates neurological conditions of DMD to other severe neurological disorders, such as schizophrenia, epilepsy and autistic spectrum disorders, among others. This review discusses the organization and the role of the dystrophin-dystroglycan complex in muscles and neurons, focusing on the neurological aspect of DMD and on the most relevant morphological and functional synaptic alterations, in both central and autonomic nervous systems, described in the pathology and its animal models.

1. Introduction

Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD) and DMD-associated dilated cardiomyopathy (or X-linked dilated cardiomyopathy, XLDCM) are a family of neuromuscular diseases characterized by common etiology, muscular wasting and several other multi-systemic alterations, commonly referred to as dystrophinopathies (Muntoni et al., 2003; Goemans and Buyse, 2014; Guiraud et al., 2015; Strehle and Straub, 2015; Ohlendieck and Swandulla, 2021; Duan et al., 2021). These dystrophies result from mutations in the *Dmd* gene encoding dystrophin, a cytoskeletal protein of 427 kDa (Dp427, full-length dystrophin) transcribed by three promoters, each active in a tissue-specific fashion, located upstream of the gene, and several short isoforms, which result from the activation of specific promoters within the *Dmd* gene and/or following alternative splicing (Blake et al., 2002; Duan et al., 2021). Common aspect among these three muscular dystrophies is a progressive muscular degeneration; however, their gravity ranges in a large spectrum from mild to severe, which lies as much in the age of onset and rapidity of progression, as in how many other tissues and organs are affected (Gosar et al., 2021). Major point of

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discrimination is certainly the number of exons affected along the large *Dmd* gene, considering that two-thirds of the mutations in DMD and BMD are deletions of one or many exons. In DMD, deletions cause a frameshift, which result in the absence of Dp427 and, in most cases, of one or more isoforms, as detailed in the following paragraph (Blake et al., 2002; Duan et al., 2021). Deletions in several exons have also been described for the XLDCM (reviewed in Nakamura, 2015).

The *Dmd* gene is localized on the chromosome Xp21 and because of this localization dystrophinopathies dominantly affects males, while female are asymptomatic carriers or mildly affected in both severity of lesions and age of onset (Grain et al., 2001). However, as introduced above, muscles (skeletal, cardiac, and smooth) are not the only tissues to be affected. Over the years it has become increasingly clear that neuromuscular pathologies are associated with other multi-system physiological alterations (Goemans and Buyse, 2014; Strehle and Straub, 2015), some of which with such a high recurrence that they could be considered real comorbidities (Ohlendieck and Swandulla, 2021). In this multi-system pathophysiological picture, the nervous system emerges as one of the most compromised. From the first pioneering studies in the sixties (Allen and Rodgin, 1960; Worden and Vignos Jr, 1962; Murphy et al., 1964; Dubowitz, 1965; Zellweger and Niedermeyer, 1965; Rosman and Kakulas, 1966; Zellweger and Hanson, 1967; Dubowitz and Crome, 1969; Prosser et al., 1969) increasing evidence from patients and natural animals model of dystrophies led to the convincement that this type of pathology was also associated with mental disabilities of various nature and degree of severity. In the following twenty years, giant steps were taken in identifying different forms of cognitive impairment (Vignos Jr., 1977; Dubowitz, 1979; Leibowitz and Dubowitz, 1981), from intellectual disability (Kozicka et al., 1971; Robinow, 1976), to early verbal impairment (Marsh and Munsat, 1974; Karagan and Zellweger, 1978). These results were the first to undermine the belief that the neurological alterations observed in dystrophic patients were a "side effect" of their health and psychosocial conditions (Gowers, 1879; Morrow and Cohen, 1954; Walton and Nattrass, 1954; Schoelly and Fraser, 1955; Truitt, 1955) and triggered the long series of studies that today have defined some of the key mechanisms underlying neuronal physiological alterations in muscular dystrophies.

Among these three dystrophinopaties, DMD is the most severe, characterized by early onset (diagnosis around 4 years of age), fast progression, and early mortality. In addition, DMD is the one presenting the highest number of cases with neurological disorders of various types and degree. These can go beyond the sphere of cognitive disabilities and with manifestations so severe as to retrace clinical aspects of autism spectrum disorders, schizophrenia, epilepsy, behavioral instabilities and much more (Melo et al., 1993; Pane et al., 2012; Ricotti et al., 2015; Astrea et al., 2015; Hendriksen et al., 2018), as it will be detailed below. The BMD is a milder form of muscular dystrophy compared to DMD, characterized by late onset (around 12 years) and a more benign and slower course, with some patients not manifesting symptoms until late in life. This pathological evolution resides on the preserved expression of a truncated, but functional, form of Dp427. Despite this, BMD patients could manifest a certain degree of mental impairment (Emery and Skinner, 1976; Zatz et al., 1993; Emery, 2002), although at a lower rate compared to DMD. Schizophrenia and attention deficit have been described in BMD patients characterized by “in-frame” deletions in the *Dmd* gene (Zatz et al., 1993; Abe et al., 1990; Beggs et al., 1991) and absence of the Dp140 isoform in brain has been associated to intellectual disability (Bardoni et al., 1999; Bardoni et al., 2000). A significant incidence of epilepsy in 7.54% *versus* 0.5% of the general pediatric population (Cowan et al., 1989) has also been described in BMD (Goodwin et al., 1997). So far, no neurological disorders have been reported as associated to the XLDCM caused by mutations in the *Dmd* gene.

Because of its social impact and dramatic diversification of the effects on the nervous system, in this review we will focus on the morpho-functional aspects underlying many of the cognitive disabilities and neurological disorders associated with DMD, taking into consideration both central and autonomic nervous systems. From this analysis of the literature it emerges, in an increasingly convincing way, how the different neurological disabilities associated with DMD derive largely from alterations of synaptic connections. These alterations are established during embryonic development, revealing a neurodevelopmental pathological side of DMD.

1.1. Duchenne muscular dystrophy: the pathology and its genetic

DMD is a rare, autosomal recessive X-linked neuromuscular diseases, affecting 1:5000 born males (Mendell et al., 2012; Ryder et al., 2017; Crisafulli et al., 2020) and caused by defective expression of a cortical cytoskeletal protein of 427 kDa (Dp427), named dystrophin (Koenig et al., 1987; Hoffman et al., 1987; Blake et al., 2002; Mercuri et al., 2019). The DMD gene encoding Dp427 is the largest described in the human genome (2.5 Mb of the Xp21) and one of the first genes to be identified by positional cloning (Koenig et al., 1988). Its discovery and characterization lead to the identification of other genes, whose mutations are causative of different types of muscular dystrophies. Laminopathies, titinopathies, dystrophinopathies and dysferlinopathies are all neuromuscular diseases, which take their names by the gene hosting distinctive mutations (Davies and Nowak, 2006). DMD is a dystrophinopathy, as the BMD and the XLCM, whose distintive pathological phenotypes derive from different mutations occurring on the same gene.

The genetics of DMD is diversified, as the abolition of Dp427 expression may depend on frameshifting mutations, as deletions (60-70%), duplications (5-15%) and point mutations (20%), as well as nonsense mutations (Mendell et al., 2012), modulated by epigenetic mechanisms (e.g., histone acetylation) (García-Rodríguez et al., 2020). The result is the lack of synthesis of the full-length dystrophin, which in skeletal muscles determines a progressive and lethal degeneration. First symptoms of the pathology manifest between the ages of 2-4 years and include gross motor delay, unsteadiness with frequent falls, waddling gait, difficulty in rising from the ground, climbing stairs and running (Ryder et al., 2017). Muscle damage progresses to the point where the young patient is wheelchair-bound by the age of 12. In several cases, language, or general developmental delay, have also been described (Gowers, 1879; Dubowitz, 1978; Jennekens et al., 1991; Emery, 1993; Emery, 2002). Other muscles, as diaphragmatic and intercostal respiratory muscles, smooth muscles and cardiomyocytes are also affected by the pathology, although with a later onset and a slower progression of symptoms compared to skeletal muscles. Degeneration of these muscles will determine progressive respiratory impairment, gastrointestinal disturbances and DMD-associated dilated cardiomyopathy. Patients die young because of respiratory and/or cardiac failure; however, with the introduction of new and improved therapies, and a lot of effort spent in care giving and management of the patients, life expectancy has raised from 20s to 40s (Kieny et al., 2013).

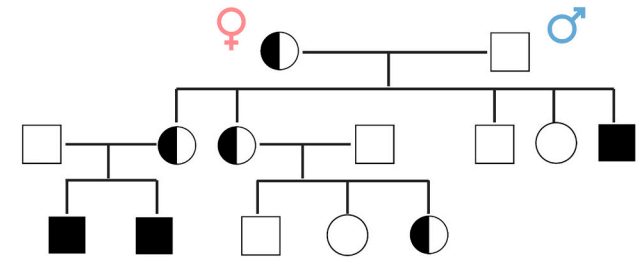
As previously mentioned, women are carriers of the disease, as they bear DMD mutations only on one X chromosomes, and for the most part are asymptomatic. However, milder forms of dystrophy, like the BMD, are rarely observed and even more rarely (less than 1 over a million) are the women severely affected (Lim et al., 2020). In these cases, DMD is either associated to the Turner syndrome, or induced by processes of translocations involving the DMD gene, or by mutations of both alleles (Ishizaki et al., 2018). More in depth details on the DMD epidemiology, genetics and muscular pathophysiology are reported in recent reviews (Duan et al., 2021).

1.2. Duchenne muscular dystrophy: the gene, the protein product and the dystrophin-dystroglycan complex

Dp427 transcription on the DMD gene is driven by three promoters, which are functionally active in different types of cells: the M promoter, active in skeletal and cardiac muscles, the P promoter, active in the

cerebellar Purkinje cells, and the B promoter, active in hippocampus and cortex (Sadoulet-Puccio and Kunkel, 1996; Blake et al., 2002; Muntoni et al., 2003; Ohlendieck and Swandulla, 2021) (Fig. 1). The protein products of the three promoters differs only for a few amino acids at the N-terminus, which contains a 5' untranslated region and the first coding exon and are functionally similar. The same gene also encodes several N-truncated dystrophin isoforms, named accordingly to their molecular mass (Dp260, Dp140, Dp116, Dp71 and Dp40), transcribed from different internal promoters located in the introns upstream of exons 30 and/or by alternative splicing (Blake et al., 1999, 2002; Ohlendieck and Swandulla, 2021). Dystrophin isoforms are usually undetected in adult skeletal muscles, but are expressed in various cell types, as selective populations of brain (Dp140; Dp71; Dp45) (Lidov et al., 1995; Naidoo and Anthony, 2020; Romo-Yáñez et al., 2020), retina (Dp260, Dp140; Dp71) (Ueda et al., 2000; Wersinger et al., 2011; Omori et al., 2012a, 2012b) and autonomic (Lombardi et al., 2017) neurons, Schwann cells (Dp116) (Matsuo et al., 2017; Mahyoob Rani et al., 2019), kidneys (Dp140) (Lidov and Kunkel, 1998) and other tissues (Ohlendieck and Swandulla, 2021).

Dp427 belongs to the α-actinin-β-spectrin family of proteins [dystrophin, utrophin, dystrophin-related protein 2, α- and β-dystrobrevin (DB)], characterized by a long central rod domain of spectrin-like repeats, an N-terminus containing F actin-binding sites and a C-terminal region containing three large domains: the WW domain, the EF/ZZ domain within a cysteine-rich domain, and the coiled coil (CC) domain at the C-terminus (Blake et al., 2002; Ohlendieck and Swandulla, 2021) (Fig. 2). In skeletal muscles, Dp427 is the only dystrophin isoform expressed and, when evidenced by immunohistochemistry, it typically decorates the entire sarcolemma (Davies and Nowak, 2006). Here full-length dystrophin strictly associates, through its C-terminus, to a large glycoprotein complex (the dystrophin glycoprotein complex, DGC), characterized by a central protein doublet formed by the extracellular α-dystroglycan (α-DG, 120 kDa) and the transmembrane β-dystroglycan (β-DG, 43 kDa), and by several other transmembrane (α,β,γ,δ sarcoglycans, sarcopsan) and intracellular (α1,β1 syntrophins, α-DB) structural proteins. More specifically, Dp427 binds to the last 15 amino acids of the β-DG C-terminus through its Cys-rich domain, and to the cortical actin cytoskeleton through its N-terminus domain and part of the rod domain (Fig. 3A). Through this domain, it also binds to intermediate filaments and microtubules, assuming a role of important cytolinker (Prins et al., 2009). The extracellular portion of β-DG covalently bind to α-DG, that in turn forms multiple, calcium-dependent bonds with extracellular matrix proteins as laminin, agrin, and perlecan with variable affinities. In addition, the C-terminus domain of dystrophin binds to syntrophins and α-DB. Altogether, these interactions form a structural bridge between the actin cytoskeleton and the extracellular matrix, whose function is to protect the sarcolemma from tearing forces of contraction and relaxation. In addition, this central core of the DGC associates to several other cytoplasmic proteins (syncoilin, desmin, dysferlin, affixin, dysbindin) deputed to the linkage between the complex, sarcomeres and other transmembrane/signaling proteins, like integrins (Blake et al., 2002; Davies and Nowak, 2006). In dystrophin-deficient muscles, the DGC is no longer properly stabilized and disassembles, causing progressive ruptures to the plasma membrane ("delta lesions"), entry of calcium ions, with consequent metabolic alterations and activation of calcium-dependent calpain proteases and phospholipase A2, and ultimately muscle necrosis (Turner et al., 1988; Ervasti et al., 1990; Millay et al., 2008). This "sub-sarcolemmal hypothesis" is so far the most accredited, which however does not exclude other concomitant events, as muscle functional ischemia (Sander et al., 2000) and free radical damages (Prins et al., 2009; Prosser et al., 2011; Khairallah et al., 2012). Nonetheless, the DGC has not just a structural function, since it also binds to many



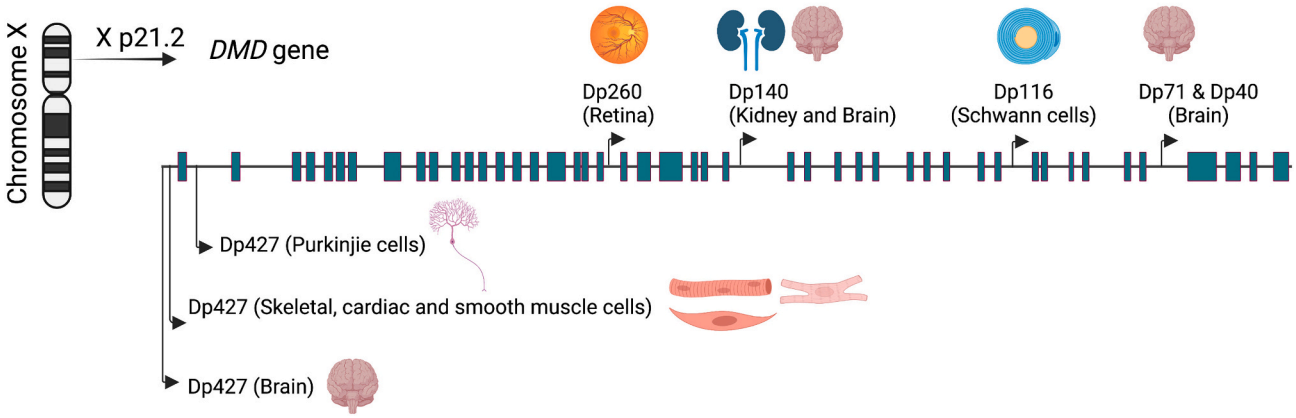


Fig. 1. The DMD gene an X-linked recessive inheritance. Schematic representation of the DMD gene, localized on the X chromosome (locus Xp21.2) showing the positions of the seven promoters driving the expression of: three full-length dystrophin (Dp427) isoforms (specifically active in brain, muscles and cerebellar Purkinje cells), Dp260, Dp140, Dp116, Dp71 and Dp40. Preferential tissues of expression for each isoform are indicated.

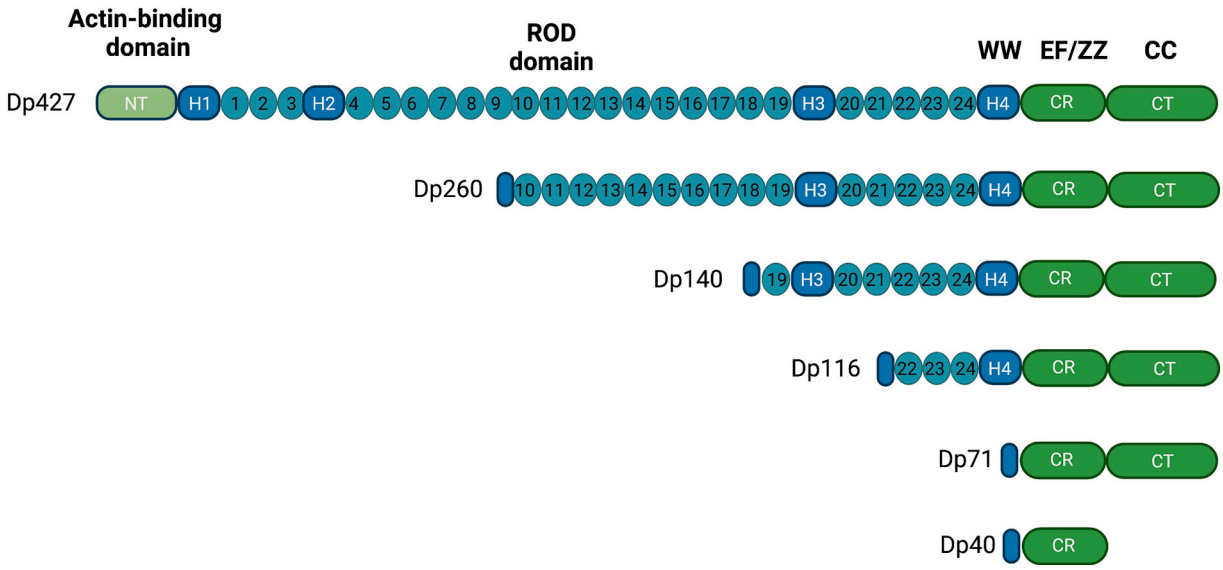


Fig. 2. Dystrophin and its isoforms. Dystrophin isoforms have similar modular organization consisting of: the N-terminus (NT), which contain actin-binding sites; the long central rod domain formed by β-spectrin-like repats and proline-rich hinge regions (H1-H4), and that is predicted to form triple-helical coiled-coils; the WW domain (WW), the ZZ domain (EF/ZZ), located in the cysteine-rich region (CR) and the coiled-coil domain (CC) in the C terminus (CT). Through this protein domains, the C-terminal region bind to some of the components of the dystrophin-associated protein complex. The Dp427 and the short isoforms differ in the length of the rod domain.

diversified signaling molecules, such as caveolin 3 (Cav3), growth factor receptor-bound protein 2 (Grb2), insulin receptor, ErbB4 receptor tyrosine kinase, stress-activated protein kinase-3 (SAPK), and various other kinases and enzymes, like the neuronal nitric oxide synthase (nNOS) (Fig. 3A). Several crucial ionic channels as the voltage-gated Na^+ channels (Nav), the inward rectifier K^+ channels (irK) and the voltage-sensing L-type Ca^{2+} channels (Cav) are also connected and stabilized into the plasma membrane by the DGC (Yang et al., 1995; Davies and Nowak, 2006; Friedrich et al., 2008; Sabourin et al., 2009; Leyva-Leyva et al., 2018). Delocalization of nNOS following DGC destruction, implies reduction in NO synthesis, with consequent decrease in protein nitrosylation and NO-mediated intracellular signaling; this intracellular path is one the most accredited causes for the functional implications associated to dystrophin-deficient muscle degeneration (Davies and Nowak, 2006; Duan et al., 2021).

Lack of Dp427 in DMD is also responsible for several pre- and post-synaptic pathophysiological alterations described at the neuromuscular junction (NMJ), although the controversy on whether these alterations followed muscle degeneration or were a direct consequence of the loss of Dp427 have been going on for decades. In mature mammalian NMJs, Dp427 is abundantly revealed at the troughs of the postsynaptic membrane, in colocalization with the Nav herein stabilized (Wood and Slater, 1998). Utrophin, a homologous of dystrophin binding to the same glycoprotein complex and expressed earlier during development, is instead localized at the crests of the junctional folds, where it is implicated, along with other proteins, in the clustering of the post-synaptic nicotinic acetylcholine receptors (nAChRs) (for review see Pilgram et al., 2010). Morphologically, NMJs of DMD patients and animal models of the disease have reduced postsynaptic fold size and are characteristically fragmented (Jerusalem et al., 1974; Harriman, 1976; Sakakibara et al., 1977; Lyons and Slater, 1991; Kong and Anderson, 1999). These alterations are successfully reduced in minidystrophin (minidysGFP) transgenic *mdx* mice (Banks et al., 2009), suggesting a major role for Dp427 in synaptic fold maturation and Nav stabilization, with a stronger influence on NMJ organization deputed to the lateral muscle cytoskeleton (Banks et al., 2009). Despite these evident structural alterations, nAChRs in dystrophic muscles do not spread in the extra-junctional area. However, *in vitro* experiments reported reduction in both spontaneous and agrin-induced nAChR clustering, with a 72% specific reduction in the number of large ($> 10\ \mu m^2$) receptor clusters in *mdx* mouse-derived myotubes compared to wild type (Kong and Anderson, 1999). This has suggested that Dp427 is not essential for initiating receptor clustering, but rather for the organization of small clusters into larger ones. Differences in the pattern of innervation during development, consisting in the progressive elimination of early outnumbered NMJs, are also observed, with *mdx* mouse fibers acquiring single innervation earlier than wild type mice (Minatel et al., 2003). The presynaptic element of a dystrophic NMJ is also affected, characterized by an age-dependent increase in nerve terminal branching, which however could be possibly influenced by the described postsynaptic fragmentation (Pratt et al., 2015). From a functional perspective, early electrophysiological studies reported no significant differences in the amplitude and frequency of miniature end-plate potentials (mEPP), or in the amplitude of evoked endplate potentials (EPP), or in neurotransmitter quantal release, with discrepancies on data related to the resting membrane potential (Sakakibara et al., 1977; Nagel et al., 1990; Lyons and Slater, 1991). However, more recent studies on *mdx* mice demonstrated a reduction in both mEPP and EPP amplitudes, as well as a depression of the safety factor, and an increase in EPP rise and quantal content (van der Pijl et al., 2016, 2018). Taken together, these data demonstrate a pivotal role of Dp427 in both synaptic maturation and neurotransmission at the NMJ. A detailed review on NMJ alterations induced by the lack of Dp427 in dystrophic muscles can be found in Ng and Ljubicic (2020).

Dystrophin isoforms expressed by other cell types differ from Dp427 and from each other in the length of the rod domain but preserve both actin-binding properties and the C-terminal region, through which they connect to the DGC and to other cytoskeletal and signaling molecules. Dystrophin short isoforms and DGC form fully functional complexes, which acquire diversified physiological activities depending on the cell type in which they are expressed. A more focused description of the dystrophin-DGC structural and functional characteristics in neurons and glia will be addressed in sections 2.3 and 2.4.

1.3. Duchenne muscular dystrophy: neurological alterations and their anatomical, morphological and functional correlates

As introduced above, after decades of denial of the possibility of

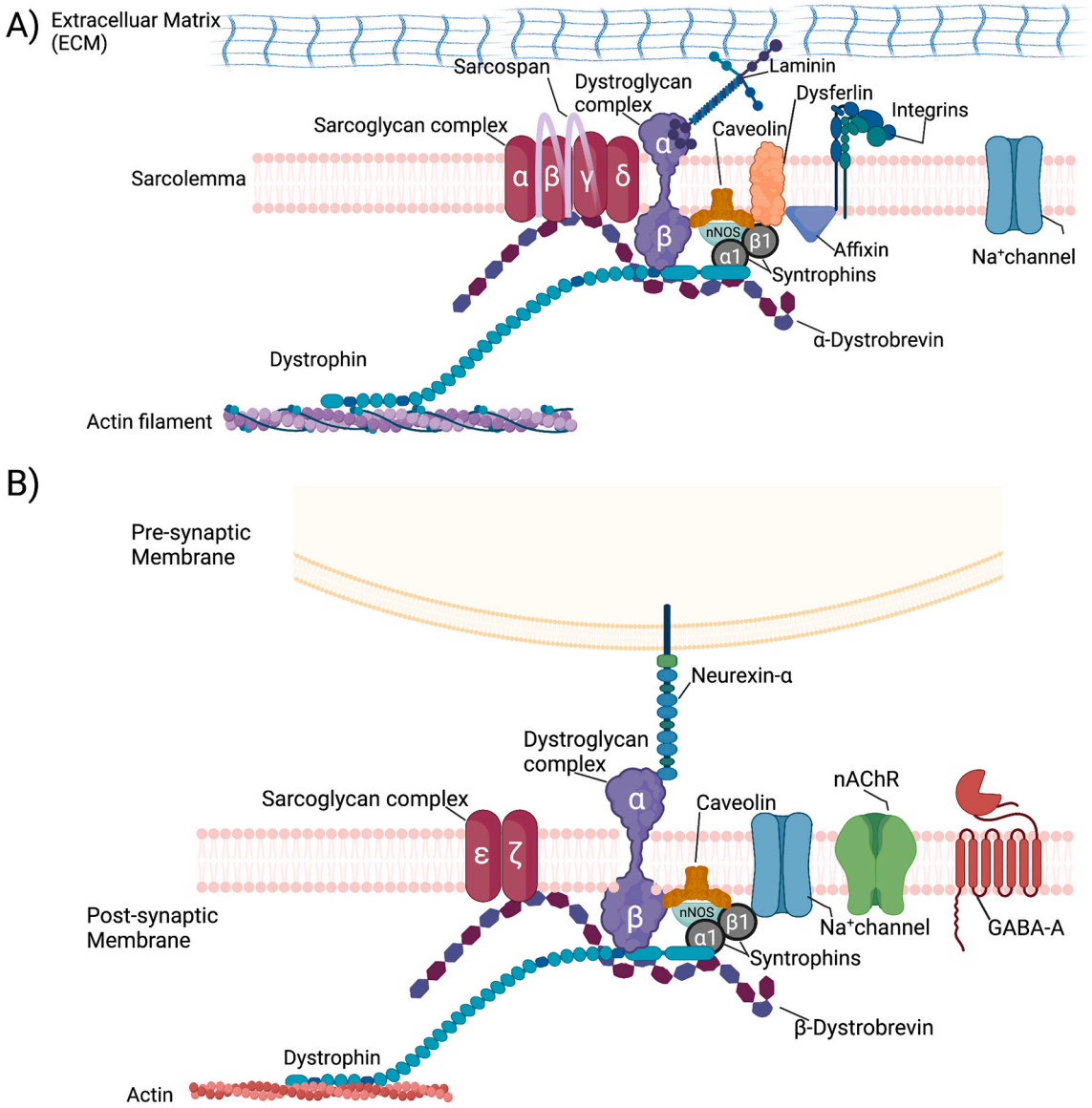


Fig. 3. Dystrophin and the dystrophin-dystroglycan associated complex in muscles (A) and neurons (B). Dp427 binds to the actin cytoskeleton through its N-terminus domain, and to several proteins of the complex through its C-terminus domain. For sake of clarity, only the principal structural and signaling components of the muscular and neuronal complexes are depicted. The molecular composition between the two complexes varies, with a major difference relying on the extracellular binding partner of α-dystroglycan, which is the laminin of the extracellular matrix in muscle, and the presynaptic protein neurexin in the nervous system. Na^+ channels (muscles and neurons), nicotinic acetylcholine receptors (nAChRs) (neurons) and $GABA_A$ receptors (neurons), stabilized by the dystrophin-dystroglycan complex, are also shown. Except for Na^+ channels, the linkage between neurotransmitter receptors and the dystrophin-dystroglycan complex is mediated by different scaffolding proteins that have not been represented.

cognitive impairment associated with DMD since Duchenne's discovery of the pathology in 1868, an extraordinary amount of clinical research has clearly brought into the light this obscure aspect of muscular dystrophy. First indications of a pathological implication of the brain in DMD came with the observation that average intelligence quotient (IQ) distribution of the DMD population is shifted by one standard deviation below the normal range scored in age-matched healthy subjects, leading to 30% of patients below 70 (Allen and Rodgin, 1960; Worden and Vignos Jr, 1962; Dubowitz, 1965, 1979; Zellweger and Niedermeyer, 1965; Rosman and Kakulas, 1966; Zellweger and Hanson, 1967; Bresolin et al., 1994; Felisari et al., 2000; Nardes et al., 2012); nevertheless, variability remains substantial among subjects, with a different impact on verbal and performance IQ (Prosser et al., 1969; Sollee et al., 1985). Throughout the years, an increasing number of investigations demonstrated the association of DMD with diverse forms of authentic neurological disorders (Mehler, 2000; Anderson et al., 2002; Cyrulnik and Hinton, 2008; Hinton et al., 2009; Waite et al., 2009; Snow et al., 2013; Piccini et al., 2014; Hendriksen et al., 2015; Hendriksen et al., 2018; Darmahkasih et al., 2020). Among these, important neurological conditions as epilepsy (Goodwin et al., 1997; Pane et al., 2013; Etemadifar and Molaei, 2004; Hendriksen et al., 2018) and several social (Hinton et al., 2006; Cyrulnik et al., 2008), neuropsychiatric (e.g., obsessive-compulsive behavior; attention deficit; autism spectrum disorders, schizophrenia) (Melo et al., 1993; Hinton et al., 2009; Pane et al., 2012; Parisi et al., 2018), behavioral (e.g., hyperactivity disorder) (Ricotti et al., 2016), cognitive (e.g., memory alteration; deficits in language abilities, visuospatial learning, reading, mathematics and spelling; impaired working memory) (Karagan et al., 1980; Dorman et al., 1988; Billard et al., 1998; Cyrulnik et al., 2007, 2008; Rae and O'Malley, 2016; Thangarajh et al., 2020) and emotional disturbances (Ricotti et al., 2016) have been characterized. The first demonstration that these neurological outcomes were indeed the product of DMD-specific organic

and genetic phenotypes, and not of the so-called "external factors", came from an accurate study by Billard and colleagues (Billard et al., 1992), who analyzed adolescent boys (12-16 years) affected by DMD (24 patients) and by spinal muscular atrophy (SMA) (17 patients), a neuromuscular disease similar to DMD in the severity and progression of motor impairment. To avoid bias in the study, young patients came from the same French region, and were matched for socio-economic conditions, motor handicap and living conditions (resident in a center or living at home). The battery of neurophysiological test administered revealed a significant impairment in DMD, compared to SMA patients, of learning abilities, such as verbal and performance intelligence, reading abilities, solving arithmetic problems, word definition, reading abilities, sentence comprehension, auditory selective attention and some memory abilities. Other parameters, as visuospatial skills were instead similar between the two groups, also strongly suggesting that specific brain regions were affected in DMD. To date, it is known that almost all neurological alterations span through a range of severity depending on the type and location of mutations within the *Dmd* gene (Bushby, 1992; Lenk et al., 1993; Pane et al., 2012; Ricotti et al., 2016; Doorenweerd et al., 2017), and therefore on the number and type of dystrophin isoforms that are affected, with the most severe phenotypes rarer than the others (Mehler, 2000; Snow et al., 2013). Based on this large amount of clinical literature data, the concept of a true "DMD neuropsychiatric syndrome" has been proposed (Ricotti et al., 2016).

The localization of Dp427 and its isoforms in brain, retina and peripheral neurons has benefitted from the use of the *mdx* mouse, a valuable rodent model for DMD. *mdx* mice carry a natural point mutation in the exon 23 of the DMD gene, which abolishes the expression of Dp427 in both male and females but preserves the expression of its short isoforms. This model is, therefore, particularly useful for investigating the specific role of the full-length dystrophin isoform on cognitive and behavioral alterations. Immunohistochemical and/or biochemical studies have shown the expression of Dp427 in specific neuronal populations of cerebral cortex (Lidov et al., 1990, 1993), hippocampus (Kim et al., 1992; Lidov et al., 1993; Anderson et al., 2002), amygdala (Sekiguchi et al., 2009; Doorenweerd et al., 2017), cerebellum (i.e., Purkinje cells) (Huard and Tremblay, 1992; Lidov et al., 1993; Briatore et al., 2020) and retina (Wersinger et al., 2011; Persiconi et al., 2020) as well as in autonomic sympathetic ganglia (i.e., superior cervical ganglion) (De Stefano et al., 1997; Lombardi et al., 2017). Localization in central neurons was also confirmed by autoptic studies on human brains, demonstrating that Dp427 was absent from cerebral and cerebellar neurons of DMD patients when compared to control brains (Uchino et al., 1994a, 1994b; Kim et al., 1995).

Lack of dystrophin in *mdx* mice is responsible for several behavioral and neurophysiological alterations, such as reduced sensitivity to nicotine-induced enhanced memory (Coccurello et al., 2002), impaired long-term spatial and recognition memory, and enhanced CA1 hippocampal long-term potentiation (Vaillend et al., 2004), impairment of both acquisition and long-term retention of cued and trace fear memories, and reduced path efficiency in the Morris water maze spatial learning (Chaussenot et al., 2015). In addition, *mdx* mice are characterized by alterations associated to posttraumatic disorders, such as altered social behavior and ultrasonic communication, which are traits typical of autism spectrum disorders (Miranda et al., 2015), increased anxiety and altered fear memories (Vaillend and Chaussenot, 2017; Comim et al., 2019), deficits on the habituation, aversive, and object recognition memory, and depression-like behavior (Comim et al., 2019). However, behavioral and neurological manifestations in *mdx* mice are milder than in DMD patients and in mdx^{3cv} mice, a *mdx* mouse variant, which carries a point mutation within intron 65 of the *Dmd* gene and lacks the expression of all short dystrophin isoforms (Im et al., 1996; Willmann et al., 2009).

Differently from muscular degeneration, behavioral and neurological complications associated to DMD are not progressive, indicating that the underlying neuroanatomical, molecular, and functional alterations arise at fetal stages and at birth, thus strictly related to neurodevelopment.

The lack of Dp427 alone affects development (Sbriccoli et al., 1995; Carretta et al., 2001; De Stefano et al., 2005; Licursi et al., 2012; Lombardi et al., 2017; Persiconi et al., 2020), connectivity (Vaillend et al., 1999a, 1999b; Del Signore et al., 2002; Anderson et al., 2003; Vaillend and Billard, 2002; Vaillend et al., 2004; Briatore et al., 2020;), and physiology (i.e. cognition, behavior, stress response) (Mehler et al., 1992; Mehler and Kessler, 1998; Vaillend et al., 1999a, 1999b; Anderson et al., 2002; Coccurello et al., 2002; Vaillend et al., 2002; Vaillend et al., 2004; Di Angelantonio et al., 2011; Fragapane et al., 2020; Comim et al., 2019; Caudal et al., 2020) of selected autonomic and central neurons. Particularly affected are neural circuits involved in the processing of fear response, as lack of full-length dystrophin in *mdx* mice significantly enhances fearfulness associated to mild stress and induces delayed fear learning and memory (Goyenvalle et al., 2015; Razzoli et al., 2020; Sekiguchi et al., 2009; Vaillend and Chaussenot, 2017).

A neurological disorder quite frequent in DMD patients, which could arise from the lack of the sole Dp427, is epilepsy (focal epilepsy, generalized tonic-clonic seizure and absence epilepsy). According to the size of the cohorts of subjects examined and the type of tests administered, 6.3% to 12.3% of DMD patients are also affected by epilepsy (Etemadifar and Molaei, 2004; Pane et al., 2013; Hendriksen et al., 2015; Hendriksen et al., 2018) compared to general pediatric population (0.5%-1%) (Cowan et al., 1989). Of these, 3.7% carry mutations upstream exon 31, therefore lacking only Dp427, another 7.5% of patients carry mutations between exons 31 and 61 (which could affect both Dp427 and Dp140), and none of them show mutations downstream exon 63, which potentially affect all dystrophin isoforms (Hendriksen et al., 2015). An association between DMD and West syndrome has also been reported in three patients (Cardas et al., 2017; Peña-Padilla et al., 2021), including this syndrome in the neuropsychiatric spectrum of DMD. This would rely on a large deletion involving both *Dmd* (Xp21.2) and *Arx* (Xp22.13) genes, where *Arx* mutations associate to severe epileptic encephalopathies, including West syndrome (Kato et al., 2004). The main cause for this prevalent association between DMD and epilepsy is indicated in a significant unbalanced excitatory *versus* inhibitory activity of those brain areas (cortex, hippocampus, cerebellum), in which the inhibitory synapses containing $GABA_A$ receptors are structurally and functionally stabilized by the specific association of Dp427-DGC and proteins accessory to the complex. This specific synaptic unbalance will be discussed in section 2.4. However, irrespective of whether DMD patients lack Dp427 or both Dp427/Dp140, they all are at high risk in developing comorbidities with attention deficit hyperactivity disorders, obsessive-compulsive disorders and sleep disorders, compared with non-epileptic DMD patients (Hendriksen et al., 2018).

As previously said, large part of the studies on both DMD patients and animal models indicate an important role in neurological and neuropsychiatric aspects of the pathology of short dystrophin isoforms, with a special focus on Dp71 and Dp140. Dp71 is the most abundant dystrophin isoform expressed in the mature brain by both neurons and glia (Lederfein et al., 1992; Jung et al., 1993; Tadayoni et al., 2012). Because of this widespread distribution, its functional roles are quite diversified, indicating the lack of this isoform as an aggravating, or totally responsible, factor for important neurological impairments. Absence of Dp71 in patients and animal models (Dp71-null mice) is linked to intellectual disability (Daoud et al., 2009a; de Brouwer et al., 2014; Naidoo and Anthony, 2020), spatial learning deficits (Daoud et al., 2009a), and alterations of prefrontal cortex excitation-inhibition balance and executive functions (Chaussenot et al., 2019). Several studies on the Dp71-null mouse model have indicated in the lack of postsynaptic Dp71 the major cause in several neurological disturbances, as it will be discussed in the following section.

Nevertheless, abundant and specific expression of Dp71 in cells other than neurons, and sites other than synapses, depicts multifaceted functions of this isoform in brain physiology. Dp71 is particularly enriched at

the endfeet of perivascular brain astrocytes, retinal Müller cells and cerebellar Bergman glia, where it stabilizes the water channel aquaporine-4 (AQP4) (Nagelhus et al., 1999; Fort et al., 2008; Belmaati Cherkaoui et al., 2021) and the inward rectifier K^+ channel Kir4.1 (Nagelhus et al., 1999; Connors et al., 2004; Fort et al., 2008) (Fig. 4), implicated in osmoregulation and potassium buffering, respectively. In these cells, Dp71 would form a complex with β-dDG and α1-syntrophin at GM1-cholesterol-enriched plasma membrane domains; however, in other regions, Dp71 could be substituted by Dp427 or utrophin (Connors et al., 2004; Fort et al., 2008; Belmaati Cherkaoui et al., 2021), highlighting the peculiar heterogeneity that characterizes the gliovascular units. It has been demonstrated that the lack of Dp71 at the endfeet of pericapillary astrocytes induces a drastic reduction (70%) of AQP4 aggregates in both cerebellum and hippocampus, along with a partial diminution of β-DG and complete loss of α1-syntrophin (Belmaati Cherkaoui et al., 2021). The decline of functional water channels impairs water exit from astrocyte, inducing cellular swelling, impairment of proper perivascular drainage of ions and neuro-gliovascular dysfunction (Frigeri et al., 2001; Nicchia et al., 2004; Anderson et al., 2012; Binder et al., 2012) (Fig. 5). Furthermore, loss of Dp71 prejudices K^+ buffering through the Kir4.1 channels (Connors et al., 2004) (Fig. 5), although abnormal accumulation of extracellular K^+ may also depend on the described alteration in water homeostasis by astrocytes. Unbalanced water and K^+ homeostasis, along with Dp71-dependent enhancement of the glutamatergic transmission (described in section 2.4), have been proposed as potential mechanisms contributing to dysregulation of the excitation/inhibition ratio towards neuronal overexcitation (Binder et al., 2012; Helleringer et al., 2018) and consequent increased risk of developing epilepsy and cognitive impairment (Eid et al., 2005; Binder et al., 2012; Hendriksen et al., 2015). Following the demonstration of different splice variants (14 in total) with diversified subcellular localizations (e.g. neurites, growth cones, plasma membrane, nucleus), several other roles have been attributed to Dp71 (e.g. neurite growth and differentiation, cell adhesion, organization of excitatory synapses, nuclear scaffolding and DNA repair), as excellently reviewed by Naidoo and Anthony (Naidoo and Anthony, 2020), thus confirming its importance in both neurodevelopment and mature nervous system.

Similar to Dp71, loss of the Dp140 isoform, the most expressed dystrophin isoform in the fetal human and mouse brain (Lidov et al., 1995; Morris et al., 1995; Doorenweerd et al., 2017), has been associated to severe forms of cognitive impairment in both DMD (Billard et al., 1992; Bardoni et al., 2000; Felisari et al., 2000; Ricotti et al., 2016; Tyagi et al., 2020; Battini et al., 2021) and BMD (Chamova et al., 2013). However, although about 63% of DMD patients have mutation in the central part of the *Dmd* gene, experiencing loss of both Dp427 and Dp140, the neurodevelopmental consequences of the lack of Dp140 are still under investigation. Several studies report on its localization in vascular elements and glia, among which oligodendrocytes (Lidov et al., 1995; Aranmolate et al., 2017; Caudal et al., 2020), and on its putative role in neuronal differentiation, axonal growth, dendritic development and myelinogenesis (Aranmolate et al., 2017; Doorenweerd et al., 2017). Recently, a work on *mdx52* mice (Saoudi et al., 2021), a mouse model with a deletion in exon 52 of the *Dmd* gene and deficient in both Dp427 and Dp140 (Araki et al., 1997), has demonstrated that these mice are more impaired in learning a Pavlovian association of conditioned-unconditioned stimuli during fear conditioning and have higher disturbance of emotional behavior compared to *mdx* mice. Despite further investigation is needed to explore the morpho-physiological counterpart of this phenotype, the *mdx52* mouse represents a good preclinical animal model to explore more in depth the role of Dp140 in DMD-related cognitive impairment.

Particular mention also deserves Dp40, the smallest and the last of the dystrophin isoforms to have been described, a NH_2-terminal partial product of Dp71 produced from alternative splicing, which lacks the characteristic C-terminal region (Tinsley et al., 1993). It is, therefore, presumed that most of the DMD patients with mutations in exon 63–69, characterized by severe intellectual disability, are deprived of both Dp71 and Dp40 (Daoud et al., 2009b). The raise of specific antibodies directed against Dp40 (Tozawa et al., 2012; Fujimoto et al., 2014), allowed to demonstrate that this isoform is expressed early in neonatal stages and throughout adulthood (Fujimoto et al., 2014). Furthermore, by combining biochemical (cell fractionation, affinity chromatography, immunoprecipitation) and immunocytochemical analyses on brain lysates and primary hippocampal neuron cultures, respectively, Dp40 was demonstrated to associate with presynaptic proteins like syntaxin1A, SNAP25 and CAMK II (calcium calmodulin kinase II), suggesting a role in vesicle exocytosis (Tozawa et al., 2012). However, further biochemical analyses, specifically conducted on cultured hippocampal neurons, demonstrated a prevalent somatodendritic and nuclear localization of

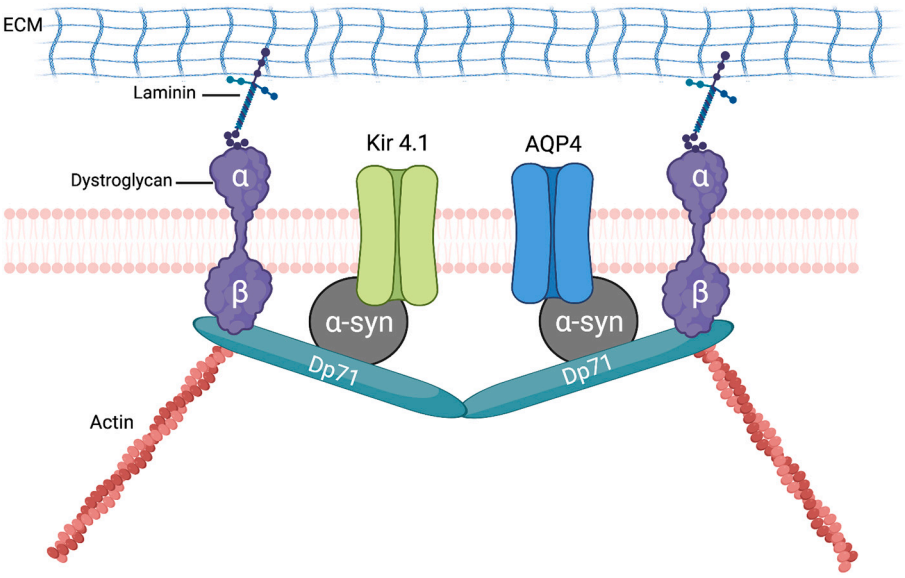


Fig. 4. Presumptive model for AQP4 and Kir4.1 stabilization by the Dp71-dystroglycan association in brain perivascular astrocytes. Dp71 is connected to the actin cytoskeleton and associates with α-syntrophin (α-syn) and β-dystroglycan, which in turn bids to the extracellular α-dystroglycan. This, by binding laminin in the extracellular matrix (ECM) stabilizes the entire complex. Kir4.1 and AQP4 link directly to α-syn within a same complex.

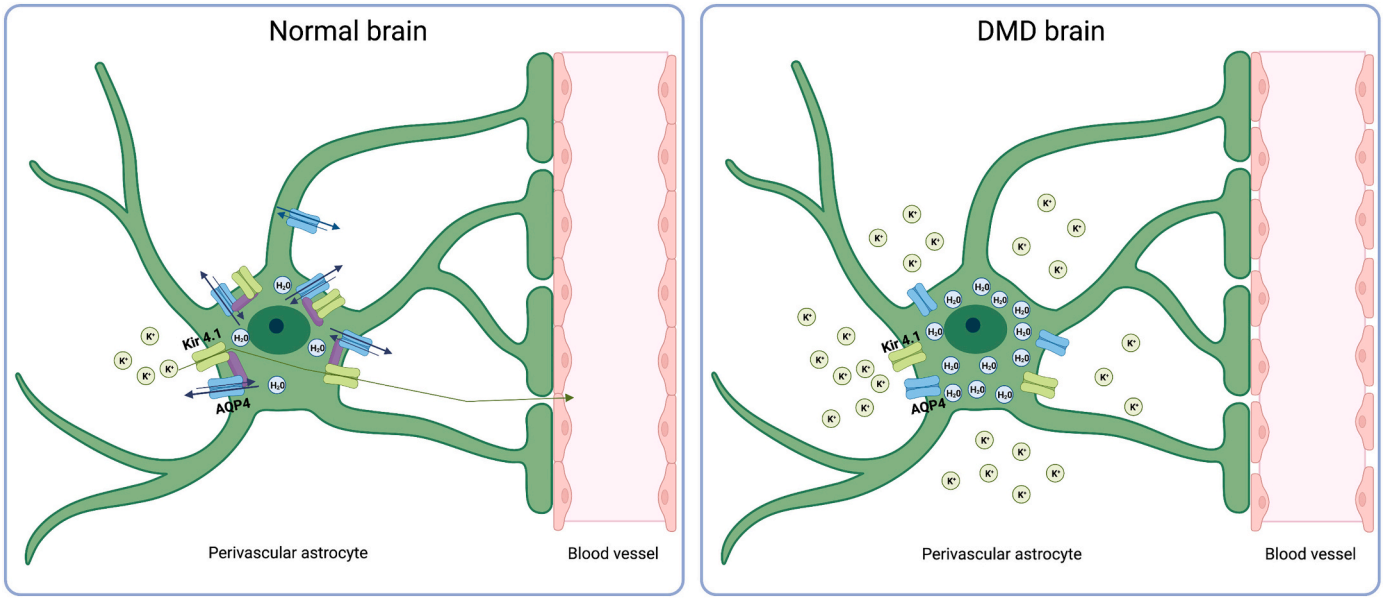


Fig. 5. Altered water homeostasis and K^+ buffering in perivascular astrocytes lacking Dp71. On the left side of the drawing, is depicted a perivascular astrocyte in normal conditions, in which AQP4 and Kir4.1 channels are stabilized by the Dp71-dystroglycan complex. This arrangement allows water homeostasis and K^+ buffering, also protecting brain blood vessels from damage. In a DMD brain (right side), disarrangement of the AQP4 and Kir4.1 channel complexes in astrocytes impairs both water homeostasis, impeding water outflow with consequent cell swelling, and K^+ ion buffering, which accumulates in the extracellular fluids contributing to neuronal hyperexcitation. Blood vessel permeability is also altered.

Dp40, and subsequent high-resolution confocal analyses showed its prominent aggregation at excitatory postsynaptic sites within dendritic spines, in co-localization with the PSD95 (Fujimoto et al., 2014). Based on these new data, the idea that Dp40 could be implicated in the post-synaptic glutamatergic transmission at hippocampal synapses has been advocated. As a matter of fact, alterations in the synaptic organization, maturation and plasticity described in the CA1 hippocampal neurons of Dp71-null mice (Miranda et al., 2011), may be in part due to the concomitant lack of Dp40. The intriguing aspect to be further investigated remains the postsynaptic protein complex to which Dp40 would associate, since it lacks the dystrophin C-terminal domain of linkage to the DGC (Tinsley et al., 1993; Tozawa et al., 2012; Fujimoto et al., 2014).

The neuroanatomical correlation to physiological and behavioral disorders in DMD, and neuromuscular diseases in general, relies on numerous clinical observations obtained by means of several imaging methods (e.g., cranial computed tomography, magnetic resonance imaging, single photon emission computed tomography, positron emission tomography ultrasound (refs. in Angelini and Pinzan, 2019). Overall, gross brain abnormalities were mainly found within the white matter, suggesting axonal disorganization (Preethish-Kumar et al., 2020), along with reduced grey matter volume and cerebral perfusion (Doorenweerd et al., 2014). These alterations were more evident in patients with DMD who lacked Dp140 than in patients who retained Dp140 expression (Doorenweerd et al., 2014). Microscopic analyses on post-mortem brains also revealed loss of cerebellar Purkinje cells, reduction of dendritic length in the visual cortex, reduced branching of apical and basal dendrites of pyramidal neurons (Jagadha and Becker, 1988), and aberrant neuroblast migration and orientation (Jagadha and Becker, 1988; Mehler and Kessler, 1998; Hatten, 1999).

In *mdx* mice, a gross and consistent anatomical disorganization is not readily apparent; however, the increased level of resolution of the anatomical-morphological analyses used has allowed to highlight several cellular and sub-cellular alterations of those neuronal populations in cerebral (hippocampus, cortex), cerebellar and autonomic districts that express Dp427 in wild type animals. Among the most striking features reported are a decrease in the density of CA1 hippocampal neurons (Miranda et al., 2016), and the significant loss of cortico-spinal (Sbriccoli et al., 1995), rubro-spinal (Carretta et al., 2001) and sympathetic neurons of the superior cervical ganglion (De Stefano et al., 2005). In addition, a reduction in the number of calretinin-expressing retinal ganglion cells in adult *mdx* mice compared to wild type, and a significant but transient dysregulation in the number of GABAergic amacrine cells during early post-natal retinogenesis have been also reported (Persiconi et al., 2020). Furthermore, lack of Dp427 severely affects adult neurogenesis in the dentate gyrus of the hippocampus, promoting cell proliferation and suppressing neuronal differentiation (Deng et al., 2009). Nevertheless, among all alterations highlighted, the most relevant pathological aspect involves the synaptic organization, as it will be discussed in the following section.

Several biochemical and metabolic modifications have also been described in DMD patients. Glucose hypometabolism, (Bresolin et al., 1994), altered bioenergetics (Tracey et al., 1995), elevated levels of choline-containing compounds (Kato et al., 1997; Rae et al., 1998) have been the first alterations described in humans. Similarly, studies on *mdx* mice, have demonstrated different biochemical and metabolic alterations compared to wild type mice. Among these are: decreased levels of brain glucose transporters, specifically in hippocampus and cerebellum, which could be linked to glucose hypometabolism (Rae et al., 2002; Wallis et al., 2004); reduced lipid and protein peroxidation, reduced catalase activity and increased superoxide dismutase activity in different brain regions (e.g., hippocampus, striatum, cortex and cerebellum), which have been proposed as a protective mechanism against increased oxidative stress (Comim et al., 2009a); dysregulation in intracellular Ca^{2+} levels in hippocampal and cortical neurons (Lopez et al., 2018); alterations of energetic metabolism (Tuon et al., 2010); reduction of acetylcholinesterase activity (Comim et al., 2011); alteration of Krebs cycle enzymes' activity (Comim et al., 2016) and reduced striatal levels of brain derived neurotrophic factor (BDNF) (Comim et al., 2009b), which could in part be responsible for reduced memory storage.

In line with the development-associated alterations induced in the nervous system by the absence of Dp427, are several observations on the superior cervical ganglion and its peripheral net of innervation within muscular (iris, ciliary body, heart) and non-muscular (submandibular

glands) targets. Loss of ganglionic neurons (De Stefano et al., 2005), impaired axonal growth and cytoskeletal dynamics *in vitro* (Lombardi et al., 2017), reduced axon defasciculation and terminal sprouting *in vivo* (De Stefano et al., 2005), alterations in the relative levels of components of the NGF signaling complex (Lombardi et al., 2008), impaired axon regeneration both *in vitro* and *in vivo* (Lombardi et al., 2017), and modulation of the expression of genes involved in neuron survival and differentiation (Licursi et al., 2012) have been demonstrated in early post-natal and adult *mdx* mice compared to wild type. Altogether, these data indicate a fundamental role of Dp427 and its complex in autonomic neuron survival, axon growth and regeneration, as well as peripheral target innervation.

1.4. Duchenne muscular dystrophy: how synaptic alterations correlate with dystrophin-associated neurodevelopmental disorders

The dystrophin-DGC preserves the same relevant function in nervous systems (in both neurons and glia) as in muscles. However, specific dissimilarities have been highlighted, in terms of type of proteins, organization, cytolinkers and localization, which herein personalize the role of this complex. The first relevant difference is the presence, in the nervous system, of the dystrophin short isoforms, which are absent in muscles. Overall, brain Dp427 account for the 10% of the protein product expressed in skeletal muscles (Anderson et al., 2012), nevertheless its absence has a deep impact on the neurobiology of DMD, as evinced in the previous section. The remnant of the protein products of the DMD gene is represented by the short dystrophin isoforms, specifically distributed among the neural cell types. In general, Dp427 is mostly expressed in brain, retina and autonomic neurons, but also found in non-neuronal cells, as oligodendrocyte (Blake and Kröger, 2000; Aranmolate et al., 2017); Dp260 is the predominant, but not exclusive, form in retinal neurons (Wersinger et al., 2011); Dp140 is mainly found in microvascular glial cells (Blake and Kröger, 2000), but also in oligodendrocytes (Aranmolate et al., 2017); Dp116 is characteristic of the peripheral myelinating Schwann cells (Imamura et al., 2000; Hnia et al., 2006; Cai et al., 2007; Matsuo et al., 2017), and the Dp71 is the most abundant isoform, significantly expressed at all life stages since embryonic development and ubiquitously distributed in neurons and glial cells of the central and peripheral nervous systems (De Stefano et al., 1997; Austin et al., 2000; Persiconi et al., 2020; reviewed in Doorenweerd, 2020). For this reason, Dp71 is, along with Dp427, the best studied isoform, and the main suspect for a large part of the neuropathological alterations associated with DMD (Naidoo and Anthony, 2020). All isoforms bind to the DGC (Blake and Kröger, 2000; Perronnet and Vaillend, 2010), except for the small Dp40 that, as previously said, lacks the dystrophin C-terminal domain (Tinsley et al., 1993). However, the DGC in the nervous system, although preserved in its basic structure, shows differences in its molecular composition, and in the interaction with transmembrane and intracellular signaling/scaffolding proteins, as well as with extracellular binding partners (Blake et al., 1999; Blake and Kröger, 2000; Perronnet and Vaillend, 2010).

In neurons as in glial cells, the DGC maintains the central structural and functional core of the β-DG/α-DG couple, but some of the other molecules can differ from those in muscles (Fig. 3B). In particular, except for the ε and ζ sarcoglycan, which have been described in brain (Zimprich et al., 2001; Shiga et al., 2006), the presence of the other four member of the family (α, β, γ, δ) has not been confirmed. In addition, α-DB is expressed in glial cells, but is replaced by β-DB in neurons (Blake et al., 1998), in which also the muscular Cav3 is substituted by Cav1 (Waite et al., 2009). α-and β-DB are encoded on different genes, and both bind directly to all dystrophin isoforms, through coiled-coil interactions, and to syntrophins (Blake et al., 1999). However, while α-DB in glial cells (e.g., perivascular astrocytes) binds to Dp71, neuronal β-DB associates to Dp427 (and other dystrophin isoforms), a complex highly enriched in post-synaptic densities (PSDs) of numerous central synapses (Blake et al., 1999), where dystrophin isoforms are stabilized through their WW domain (Sakamoto et al., 2008). Since the first description by Blake and colleagues, a significant amount of literature has described the Dp427-DGC as crucial postsynaptic component of specific cerebellar, hippocampal and cortical synapses. This localization establishes a strong structural and functional link between the molecular complex and the neural circuit functionality, by modulating synaptic activity, excitability, plasticity and signaling cascades (Perronnet and Vaillend, 2010; Hendriksen et al., 2015).

Following the first demonstrations of Dp427 localization at postsynaptic sites of central neurons (Lidov et al., 1990: Kim et al., 1992), Knuesel and collaborators showed that lack of Dp427 in the *mdx* mouse animal model induces a marked reduction in the number of postsynaptic clusters of α1- and α2-containing $GABA_A$ receptors on cerebellar (Purkinje cells) and hippocampal neurons, respectively (Knuesel et al., 1999). These results demonstrated a role for dystrophin in the clustering and/or stabilization of these specific receptors in a subset of central neurons, opening the question on whether this alteration could underlie the cognitive defects and neurological disturbances already described in DMD patients. A 40 to 70% reduction of GABAergic receptor clusters in *mdx* mouse postsynaptic densities, which were demonstrated to localize dystrophin in wild type mice, was confirmed in successive studies on cerebellum, hippocampus and amygdala (Knuesel et al., 2001; Brunig et al., 2002; Sekiguchi et al., 2009; Vaillend et al., 2010; Anderson et al., 2012), arguing in favor of a dysfunctional synaptic inhibition in these brain areas (Anderson et al., 2003; Perronnet and Vaillend, 2010), and unbalanced excitatory/inhibitory homeostasis, which underlie epileptic behaviors (Knuesel et al., 2001; Fritschy, 2008; Hendriksen et al., 2015). In addition, whole cell patch-clamp recording of spontaneous miniature inhibitory post-synaptic currents (mIPSCs) in Purkinje cells from cerebellar slices of *mdx* mice demonstrated a significant reduction in the number of synaptic $GABA_A$ receptors compared to wild type littermates. Remnant receptors, however, were functionally intact, as they retained normal channel unitary conductance, and both rise and decay of the mIPSCs (Kueh et al., 2011). Interestingly, the use of gaboxadol, a partial agonist of $\alpha1\beta2\gamma2$ receptor and selective agonist of extra synaptic $GABA_A$ receptors, further demonstrated a concomitant increase of GABA extra synaptic receptors, according to previous data reporting on unchanged gene expression and protein levels of the $GABA_A$ α1 subunit in *mdx* mouse cerebellum compared to wild type (Wallis et al., 2004; Kueh et al., 2008). These data all reaffirmed a main role of Dp427 in receptor clustering, but not in receptor assembly or activity (Vaillend et al., 2010; Kueh et al., 2011).

Further studies on the CA1 region of the hippocampus demonstrated that Dp427 at specific $GABA_A$-containing inhibitory synapses is also important for the maintenance of the entire molecular machinery that determines the precise spatial-temporal pattern of GABAergic synaptic transmission, as absence of dystrophin in *mdx* mice induces a significant rearrangement of both the pre- and postsynaptic proteins of inhibitory synapses, as well as axon terminal proteins of specific GABAergic interneurons (Krasowska et al., 2014). Among these are the adhesion molecule neuroligin 2, which by binding the presynaptic neurexin is required for proper inhibitory synapse maturation (Varoqueaux et al., 2004), and the presynaptic GABA transporter (Krasowska et al., 2014). These molecular and structural alterations in the CA1 hippocampal region determine a rearrangement of the inhibitory synaptic inputs, which could be responsible for an imbalanced circuital activity within the hippocampus with consequent enhanced long-term plasticity (Dallérac et al., 2011; Vaillend and Billard, 2002; Vaillend et al., 1999a, 1999b) and impaired spatial memory (Vaillend et al., 1998; Vaillend et al., 2004). Importantly, GABAergic efficacy of *mdx* mouse hippocampal interneurons could be improved, both *in vitro* and *in vivo*, by activation of the non-canonical *Wnt-5* signaling pathway, which specifically increases the number of inhibitory synapses and the amount of postsynaptic $GABA_A$ receptors. The functional correlations of these structural modifications were a significant increase in the amplitude of evoked IPSCs, in the frequency of spontaneous mIPSCs and in

hippocampal GABAergic efficacy, without affecting the probability of presynaptic GABA release (Fuenzalida et al., 2016).

Not all research groups working on GABAergic dysfunction in DMD evidenced differences in spatial learning or hippocampal LTP between wild type and *mdx* mice (Sesay et al., 1996; Bianchi et al., 2020), possibly because different protocols of LTP-inducing conditions. Nevertheless, a work conducted on the DBA/2J-*mdx* mouse model of DMD (generated backcrossing classical Bl/10-*mdx* mouse line onto a DBA/2J genetic background) demonstrated for the first time intrinsic alterations in the membrane excitability of CA1 hippocampal pyramidal cells, residing in a significant increase in the medium component of after-hyperpolarization (mAHP) (Bianchi et al., 2020). Longer mAHP, which determines the refractory period after an action potential, may result in reduced excitability of neural networks and, in turn, be an additional element accounting for the cognitive impairment paralleling dystrophin deficiency. Since AHP is operated through voltage gated channels (Kv), as the inward rectifier (K_{ir}), and since lack of dystrophin *via* syntrophin (Willis et al., 2015) has been indicated as responsible for several changes in K_{ir} conductance in cardiomyocytes (Rubi et al., 2017), a role for Dp427-syntrophin in docking neuronal Kv has been proposed (Bianchi et al., 2020).

If from the one hand Dp427 is important for proper $GABA_A$ receptor clustering at synapses, on the other hand a determinant contribution for receptor localization is advocated to the postsynaptic DG. Lack of DG in conditional knockout (KO) mice determines reduction of $GABA_A$ receptors and of other postsynaptic proteins, as neuroligin2 and S-SCAM, in cerebellar Purkinje cells, with consequent severe GABAergic denervation and motor learning disability (Briatore et al., 2020). Interestingly, results on postsynaptic receptor expression in *mdx versus* DG-KO mice further indicate α-DG as a major GABAergic synaptic organizer, carving out an important role for this extracellular component of the DGC in the stabilization of cerebellar GABAergic synapses (Briatore et al., 2020) (Fig. 6). A central role of DG and α -DG glycosylation in regulating GABAergic synaptic plasticity homeostasis has been also reported in hippocampal neurons, both *in vitro* (Pribiag et al., 2014) and *in vivo* (Früh et al., 2016). Impairment of DG protein synthesis, specific knock down of DG expression and reduced α-DG glycosylation *in vitro* blocks the homeostatic scaling up of GABAergic synapses (Pribiag et al., 2014), determinant in the regulation of brain functions, which relies on the reciprocal regulation of GABAergic (inhibitory) and glutamatergic (excitatory) signaling (Turrigiano, 2012). Similarly, conditional deletion of *Dag1*, which encodes dystroglycan, in pyramidal cells causes loss of a subset of specific basket cell terminals (cholecystokinin-positive basket neurons) in both hippocampus and cortex, with a reduction in the frequency of pyramidal cell inhibitory activity (Früh et al., 2016). These studies highlight the strict and reciprocal dependence between postsynaptic dystrophin and DG, at both structural and functional levels, so that the absence of either dystrophin or DG, or their functional mutations, result in muscular dystrophies with severe cognitive deficits and epilepsy (Godfrey et al., 2011; Pane et al., 2013). Recent works also demonstrated that alteration or absence of other specific components of the GABAergic postsynaptic DGC, as the inhibitory synaptic protein 1 (InSyn1), alter DGC and $GABA_A$ receptor organization, with consequent increase in neuronal excitation evidenced by perturbation of neuronal bursting *in vitro*, and defective memory retrieval in hippocampus-dependent cognitive tasks *in vivo* in InSyn1 null mice (Uezu et al., 2019).

Successive studies on the hippocampus showed, by histological analyses, an increase in the density of axodendritic symmetric inhibitory synapses and morphometric larger PSDs at the perforated excitatory synapses. These modifications suggested on the one hand a compensatory effect due to the reduction of $GABA_A$ receptor clustering, and on the other a rearrangement of excitatory synapses induced by increased excitation (Miranda et al., 2009). Reduction of GABAergic inhibitory activity in dystrophin-deficient *mdx* mice also results in the enhancement of the short-term potentiation and of the early phase of LTP driven by NMDA glutamatergic receptors (Vaillend et al., 1998; Vaillend et al., 1999a, 1999b; Vaillend and Billard, 2002). Hippocampal long-term depression (LTD), based on the activation of these same ionotropic receptors, is also impaired, as recorded after low-frequency stimulation of the Schaffer-commissural projections to CA1 neurons in *mdx* mice (Vaillend and Billard, 2002). Rescue of the dystrophin-like protein by exon skipping *in vivo* restores $GABA_A$-receptor clustering in hippocampal neurons (Vaillend et al., 2010) and normalizes synaptic plasticity (Dallérac et al., 2011). More recently, GABAergic dysfunction in Dp427-lacking mice has been functionally associated to increased anxiety and altered fear memories following a mild acute stress. This also affects the motor outcome (e.g., long-lasting motor inhibition), shedding a light on a possible relation between the role of Dp427 at inhibitory synapses and

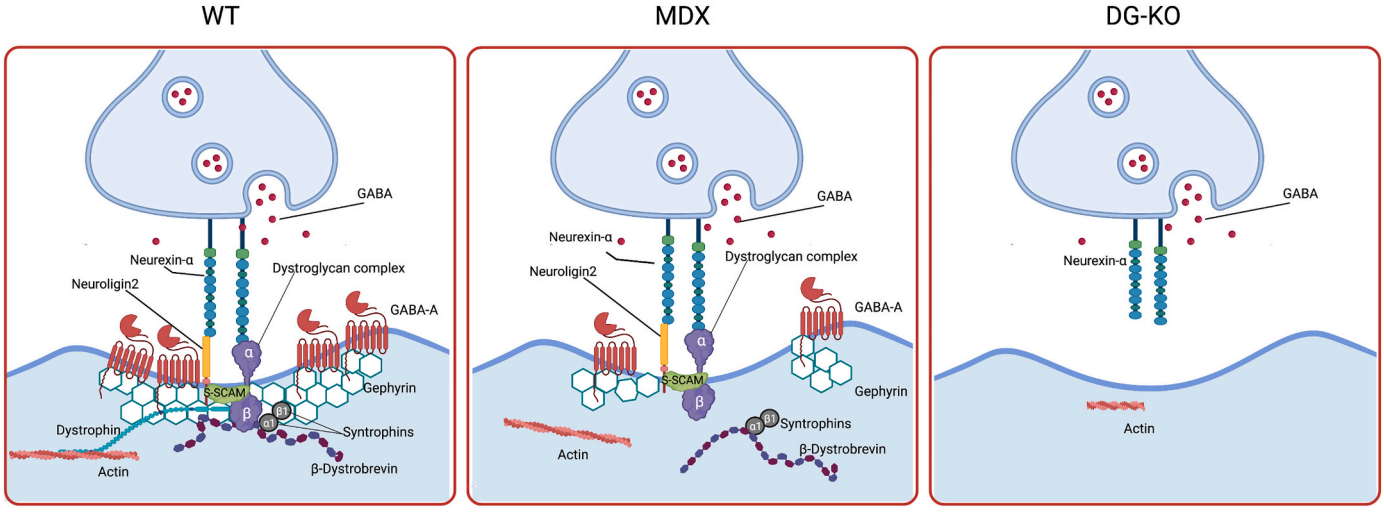


Fig. 6. Changes of the postsynaptic organization of $GABA_A$-containing inhibitory synapses on the cerebellar Purkinje cells following removal of either Dp427 or dystroglycan (DG-KO). In wild type (WT) mice, $GABA_A$ receptors are clustered within the postsynaptic specialization by binding directly to a submembranous lattice of gephyrin, connected to the Dp427-dystroglycan complex. Synapse stabilization depends on the linkage between the presynaptic protein neurexin and both the postsynaptic proteins neuroligin 2 and α-dystroglycan. Neurexin and β-dystroglycan are linked to each other by S-SCAM. In *mdx* mice, the absence of Dp427 destabilizes dystroglycan and the complex of associated proteins, with a significant reduction of $GABA_A$ receptors within the postsynaptic membrane. Other proteins, as α-dystroglycan, neuroligin. S-CAM and neurexin remain largely unaffected. Lack of DG in conditional Purkinje cell knockout mice determines disruption of GABAergic synapses and complete loss of $GABA_A$ receptors.

emotional aspects (Vaillend and Chaussenot, 2017).

A series of interesting studies on *Drosophila melanogaster*, suggested a new role for dystrophin isoforms as retrograde trans-synaptic regulators of neurotransmitter exocytosis at several synapses, including the glutamatergic ones (Bogdanik et al., 2008; Fradkin et al., 2008; van der Plas et al., 2006; Wairkar et al., 2008). This idea stemmed from increasing evidence on the strict relationship between pre- (β-neurexin) and post-synaptic (PSD95 and neuregulin) scaffolding proteins in rodent hippocampal glutamatergic synapses, which would retrogradely contribute to the control of presynaptic release probability (Futai et al., 2007). At Dp427- or Dp71-containing PSDs, synaptic stabilization is fully operated by the postsynaptic α-DG of the DGC and the presynaptic neurexins (Sugita et al., 2001; Pilgram et al., 2010). The main difference between the two isoforms is the synaptic localization, as Dp427 is classically associated to GABAergic inhibitory synapses, while Dp71 is localized at selected hippocampal excitatory synapses, where it modulates the clustering of glutamate receptors (Blake et al., 1999; Daoud et al., 2009a) (Fig. 7). Lack of this short isoform, indeed, induces significant synaptic alterations. In particular, in the cerebellum of Dp71-null mice, one of the most affected areas also in *mdx* mice and DMD patients (Cyrulnik and Hinton, 2008), the excitatory transmission at the glutamatergic synapses that inferior olivary neurons form on cerebellar Purkinje cells, is significantly enhanced, involving both AMPA and NMDA receptor activity (Helleringer et al., 2018). This is in accord to what previously observed by the same authors in the hippocampus of the Dp71-null animal model (Daud et al., 2009b). Cerebellar functional unbalance is associated with altered strategies in goal-oriented navigation, which stems from impaired synaptic plasticity and clustering of the PSD-95 (postsynaptic density protein), and suggests a direct involvement of Dp71 in the molecular organization of glutamatergic post-synaptic densities and stabilization of NMDA receptors (Daoud et al., 2009a, 2009b; Helleringer et al., 2018).

A serendipitous ultrastructural analysis of CA1 hippocampal axo-spinous non-perforated excitatory synapses in mice lacking either Dp427 or Dp71, highlighted significant alterations in the density and size of different pools of synaptic vesicles and in the synaptic cleft width, with evident differences between the two genotypes. Although the specific causative mechanisms suggested were different for the two isoforms (considering their typical synaptic localization) these studies demonstrated for the first time that the loss of either Dp427 or Dp71 impacts on the presynaptic organization of central glutamatergic synapses (Miranda et al., 2011). Corroborating a more direct role of dystrophin isoforms on the presynaptic functions are also several

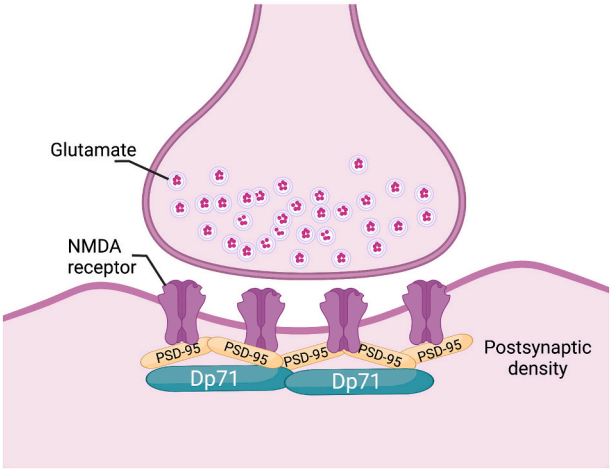


Fig. 7. Proposed role of Dp71 in NMDA receptor clustering. In selected hippocampal excitatory synapses, Dp71 has been proposed as responsible for the organization of NMDA receptors in the postsynaptic specialization. Its exact location and link with the PSD95, however, have not yet been clarified.

immunohistochemical and ultrastructural studies on the retina of different species, including human, showing expression of dystrophin (most probably Dp260) and DGC components in both pre- and post-synaptic compartments of the ribbon synapses between photoreceptors and ON bipolar cells in the outer plexiform layer (Drenckhahn et al., 1996; Schmitz and Drenckhahn, 1997; Ueda et al., 1997a, 1997b; Koulen et al., 1998; Blake et al., 1999; Jastrow et al., 2006; Omori et al., 2012a, 2012b). The presence of dystrophin-DGC in both synaptic compartments would be determinant for proper synaptic formation (Sato et al., 2008; Omori et al., 2012a, 2012b). As a matter of fact, DMD patients and animal models of the disease (*mdx*, *mdx*^{3cv}) can exhibit several visual defects, with different degrees of severity depending on the gravity of the phenotype, which may rely on dysfunctions of ribbon synapse transmission (Stockton and Slaughter, 1989; Fitzgerald et al., 1994; Barboni et al., 2013; Barboni et al., 2016).

Related to the impact that lack of dystrophin may have on the presynaptic terminal activity is the demonstration that synaptosome preparations form the cerebellum of *mdx* mice showed a reduction (47%) in [3H]-GABA release induced by nicotine application and an increase (44%) in [3H]-GABA uptake compared to wild type (Pereira da Silva et al., 2018). High K^+ depolarization did not exert the same effect, as well as no changes were seen in synaptosomes deriving from cortex or hippocampus (Pereira da Silva et al., 2018). According to the literature, nAChR activity increases GABA release in the hippocampus and other brain areas (McClure-Begley et al., 2009; Zappettini et al., 2011), and 1 year old *mdx* mice are characterized by reduced levels of hippocampal α7 and β2 subunit-containing nAChRs, compared to control (Ghedini et al., 2012). Therefore, it has been hypothesized that lack of Dp427, by inducing disassembly of the DGC and alteration of the post-synaptic membrane, would indirectly determine dysfunctional GABA release modulated by presynaptic heteromeric nAChR (possibly containing α4, α5, α7, β2 and/or β4 subunits), and this could be considered as a presynaptic mechanisms adjusting GABAergic synaptic transmission following reduced $GABA_A$ receptivity (Pereira da Silva et al., 2018). Notably, *mdx* mice have also been demonstrated to be less responsive than wild type to nicotine administrations in a post-training nicotine challenge during a passive avoidance test, further highlighting functional changes in central nAChR of dystrophic mice (Coccurello et al., 2002).

Synaptic alterations have also been described for the autonomic neurons of the sympathetic superior cervical ganglion. This class of peripheral neurons expresses Dp427, other short dystrophin isoforms (Dp260, Dp71) (De Stefano et al., 1997), α-DG and β-DG (Zaccaria et al., 1998, 2000). Dystrophin and DGs immunolabeling is associated with several cell organelles and specific plasma membrane domains of neuronal cell body and axon, as well as within numerous PSDs of the cholinergic synapses that preganglionic neurons establish on the sympathetic neurons. Here the Dp427-DGC is involved in the physical stabilization of pre- and postsynaptic partners (Zaccaria et al., 1998) as well as of postsynaptic clusters of nAChR formed by α3,β2/β4 subunit association (Zaccaria et al., 2000), as demonstrated by using the *mdx* mouse model. Fast intraganglionic synaptic transmission through this specific class of nAChRs, is also affected (Di Angelantonio et al., 2011). Although underestimated, autonomic alterations would be another serious issue to consider in the DMD pathology, involving several physiological aspects, from the motor response to different stimuli, to the modulation of hypothalamus-pituitary-adrenal axis activity associated to stress responses.

2. Conclusions

Among the three dystrophinopaties, characterized by the presence of mutations in the gene encoding Dp427 and its short isoforms, DMD is the most detrimental, identified by early onset and fast progression of muscular degeneration. Cognitive and neurological disorders are typically associated to the pathology, although for many years they had been

considered as secondary complications subordinated to progressive muscular paralysis. The neurological aspect of DMD has its roots in the neurodevelopment and relies on the lack of Dp427, possibly together with one or more short dystrophin isoforms, from selected neuronal population. There is no cure for DMD, however anti-inflammatory treatments associated to specific pharmacological therapies and diverse gene therapies, aiming at restoring dystrophin production (Reinig et al., 2017; Iftikhar et al., 2021; Abreu and Waldrop, 2020), are having success in extending life prospects. Nonetheless, this could increasingly aggravate the problem of an impact of the neurological trait of DMD on the quality of life of patients. Disassembly and/or weakening of selected synaptic connections caused by the absence of Dp427, or of some other synaptic isoforms, impair the physiology of important brain (hippocampal, cortical, cerebellar) and autonomic circuits, and could represent one of future therapeutical targets for DMD.

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References

Abe, M., Arai, M., Maehara, K., Arikawa, E., Arahata, K., 1990. A case of Becker muscular dystrophy with schizophrenia symptoms. Brain Nerve 42, 1061–1066.
Abreu, N.J., Waldrop, M.A., 2020. Overview of gene therapy in spinal muscular atrophy and Duchenne muscular dystrophy. Pediatr. Pulmonol. 2020, 1–11.
Allen, J.E., Rodgin, D.W., 1960. Mental retardation in association with progressive muscular dystrophy. Am. J. Dis. Child 100, 208–211.
Anderson, J.L., Head, S.I., Rae, C., Morley, J.W., 2002. Brain function in Duchenne muscular dystrophy. Brain 125, 4–13.
Anderson, J.L., Head, S.I., Morley, J.W., 2003. Altered inhibitory input to Purkinje cells of dystrophin-deficient mice. Brain Res. 982, 280–283.
Anderson, J.L., Head, S.I., Morley, J.W., 2012. Duchenne muscular dystrophy and brain function. In: Hedge, M., Ankala, A. (Eds.), Muscular Dystrophy. Intech, pp. 91–122.
Angelini, C., Pinzan, E., 2019. Advances in imaging of brain abnormalities in neuromuscular disease. Ther. Adv. Neurol. Disord. 12, 1–24.
Araki, E., Nakamura, K., Nakao, K., Kameya, S., Kobayashi, O., Nonaka, I., Kobayashi, T., Katsuki, M., 1997. Targeted disruption of exon 52 in the mouse dystrophin gene induced muscle degeneration similar to that observed in Duchenne muscular dystrophy. Biochem. Biophys. Res. Commun. 238, 492–497.
Aranmolate, A., Tse, N., Colognato, Holly, 2017. Myelination is delayed during postnatal brain development in the *mdx* mouse model of Duchenne muscular dystrophy. BMC Neurosci. 18, 63.
Astrea, G., Pecini, C., Gasperini, F., Brisca, G., Scutifero, M., Bruno, C., Maria Santorelli, F., Cioni, G., Politano, L., Chilosi, A.M., Battini, R., 2015. Reading impairment in Duchenne muscular dystrophy: A pilot study to investigate similarities and differences with developmental dyslexia. Res. Dev. Disabil. 45-46, 168–177.
Austin, R.C., Morris, G.E., Howard, P.L., Klamut, H.J., Ray, P.N., 2000. Expression and synthesis of alternatively spliced variants of Dp71 in adult human brain. Neuromuscul. Disord. 10, 187–193.
Banks, G.B., Chamberlain, J.S., Froehner, S.C., 2009. Truncated dystrophins can influence neuromuscular synapse structure. Mol. Cell. Neurosci. 40, 433–441.
Barboni, M.T., Nagy, B.V., de Araújo Moura, A.L., Damico, F.M., da Costa, M.F., Kremers, J., Ventura, D.F., 2013. ON and OFF electroretinography and contrast sensitivity in Duchenne muscular dystrophy. Invest. Ophthalmol. Vis. Sci. 54, 3195–3204.
Barboni, M.T.S., Martins, C.M.G., Nagy, B.V., Tsai, T., Damico, F.M., da Costa, M.F., Pavanello, RdCM, Lourenço, N.C.V., Cerqueira, A.M.P., Zatz, M., Kremers, J., Ventura, D.F., 2016. Dystrophin Is required for proper functioning of luminance and red–green cone opponent mechanisms in the human retina. Invest. Ophthalmol. Vis. Sci. 57, 3581–3587.
Bardoni, A., Sironi, M., Felisari, G., Comi, G.P., Bresolin, N., 1999. Absence of brain Dp140 isoform and cognitive impairment in Becker muscular dystrophy. Lancet 353, 897–898.
Bardoni, A., Felisari, G., Sironi, M., Comi, G., Lai, M., Robotti, M., Bresolin, N., 2000. Loss of Dp140 regulatory sequences is associated with cognitive impairment in dystrophinopathies. Neuromuscul. Disord. 10, 194–199.
Battini, R., Lenzi, S., Lucibello, S., Chieffo, D., Moriconi, F., Cristofani, P., Bulgheroni, S., Cumbo, F., Pane, M., Baranello, G., Alfieri, P., Astrea, G., Cioni, G., Vicari, S., Mercuri, E., 2021. Longitudinal data of neuropsychological profile in a cohort of Duchenne muscular dystrophy boys without cognitive impairment. Neuromuscul. Disord. 31, 319–332.
Beggs, A.H., Hoffman, E.P., Snyder, J.R., Arahata, K., Specht, L., Shapiro, F., Angelini, C., Sugita, H., Kunkel, L.M., 1991. Exploring the molecular basis for variability among patients with Becker Muscular Dystrophy: dystrophin gene and protein studies. Am. J. Hum. Genet. 49, 54–67.
Belmaati Cherkaoui, M., Vacca, O., Izabelle, C., Boulay, A.-C., Boulogne, C., Gillet, C., Barnier, J.-V., Rendon, A., Cohen-Salmon, M., Vaillend, C., et al., 2021. Dp71 contribution to the molecular scaffold anchoring aquaporine-4 channels in brain macroglial cells. Glia 69, 954–970. https://doi.org/10.1002/glia.23941.
Bianchi, R., Eilers, W., Pellati, F., Corsi, L., Foster, H., Foster, K., Tamagnini, F., 2020. Hippocampal synaptic and membrane function in the DBA/2J-*mdx* mouse model of Duchenne muscular dystrophy. Mol. Cell. Neurosci. 104, 103482.
Billard, C., Gillet, P., Signoret, J.L., Uicaut, E., Bertrand, P., Fardeau, M., Barthez-Carpentier, M.A., Santini, J.J., 1992. Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. Neuromuscul. Disord. 2, 371–378.
Billard, C., Gillet, P., Barthez, M., Hommet, C., Bertrand, P., 1998. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. Dev. Med. Child Neurol. 40, 12–20.
Binder, D.K., Nagelhus, E.A., Ottersen, O.P., 2012. Aquaporin-4 and epilepsy. Glia 60, 1203–1214.
Blake, D.J., Kröger, S., 2000. The neurobiology of Duchenne muscular dystrophy: learning lessons from muscle? Trens Neurosci 23, 92–99.
Blake, D.J., Nawrotzki, R., Loh, N.Y., Górecki, D.C., Davies, K.E., 1998. Beta-dystrobrevin, a member of the dystrophin-related protein family. Proc. Natl. Acad. Sci. U. S. A. 95, 241–246.
Blake, D.J., Hawkes, R., Benson, M.A., Beesley, P.W., 1999. Different dystrophin-like complexes are expressed in neurons and glia. J. Cell Biol. 147, 645–657.
Blake, D.J., Weir, A., Newey, S.E., Davies, K.E., 2002. Function and genetics of dystrophin and dystrophin-Related proteins in muscle. Physiol. Rev. 82, 291–329.
Bogdanik, L., Framery, B., Frölich, A., Franco, B., Morne, D., Bockaert, J., Sigrist, S., Grau, Y., Parmentier, M.-L., 2008. Muscle dystroglycan organizes the postsynapse and regulates presynaptic neurotransmitter release at the Drosophila neuromuscular junction. PLoS One 3, e2084.
Bresolin, N., Castelli, E., Comi, G.P., Felisari, G., Bardoni, A., Perani, D., Grassi, F., Turconi, A., Mazzucchelli, F., Gallotti, D., Moggio, M., Prelle, A., Ausenda, G., Fazio, C., Scarlato, G., 1994. Cognitive impairment in Duchenne muscular dystrophy. Neuromuscul. Disord. 4, 113–128.
Briatore, F., Pregno, G., Di Angelantonio, S., Frola, E., De Stefano, M.E., Vaillend, C., Sassoé-Pognetto, M., Patrizi, A., 2020. Dystroglycan mediates clustering of essential GABAergic components in cerebellar Purkinje cells. Front. Mol. Neurosci. 13, 164.
Brunig, I., Suter, A., Knuesel, I., Lüscher, B., Fritschy, J.M., 2002. GABAergic terminals are required for postsynaptic clustering of dystrophin but not of GABA(A) receptors and gephyrin. J. Neurosci. 22, 4805–4813.
Bushby, K.M., 1992. Genetic and clinical correlation of Xp21 muscular dystrophy. J. Inherit. Metab. Dis. 15, 551–564.
Cai, H., Erdman, R.A., Zweier, L., Chen, J., Shaw IV, J.H., Baylor, K.A., Stecker, M.M., Carey, D.J., Chan, Y.-M.C., 2007. The sarcoglycan complex in Schwann cells and its role in myelin stability. Exp. Neurol. 205, 257–269.
Cardas, R., Iliescu, C., Butoianu, N., Seferian, A., Gataullina, S., Gargaun, E., Nectoux, J., Bienvenu, T., Craiu, D., Gidaro, T., Servais, L., 2017. DMD and West syndrome. Neuromuscul. Disord. 27, 911–913.
Carretta, D., Santarelli, M., Vanni, D., Carrai, R., Sbriccoli, A., Pinto, F., Minciacchi, D., 2001. The organisation of spinal projecting brainstem neurons in an animal model of muscular dystrophy. A retrograde tracing study on *mdx* mutant mice. Brain Res. 895, 213–222.
Caudal, D., Francois, V., Lafoux, A., Ledevin, M., Anegon, I., Le Guiner, C., et al., 2020. Characterization of brain dystrophins absence and impact in dystrophin-deficient *Dmdmdx* rat model. PLoS One 15, e0230083.
Chamova, T., Guergueltcheva, V., Raycheva, M., Todorov, T., Genova, J., Bichev, S., Bojinova, V., Mitev, V., Tournev, I., Todorova, A., 2013. Association between loss of dp140 and cognitive impairment in Duchenne and Becker dystrophies. Balkan J Med Genet 16, 21–30.
Chaussenot, R., Edeline, J.M., Le Bec, B., El Massioui, N., Laroche, S., Vaillend, C., 2015. Cognitive dysfunction in the dystrophin-deficient mouse model of Duchenne muscular dystrophy: a reappraisal from sensory to executive processes. Neurobiol. Learn. Mem. 124, 111–122.
Chaussenot, R., Amar, M., Fossier, P., Vaillend, C., 2019. Dp71-dystrophin deficiency alters prefrontal cortex excitation-inhibition balance and executive functions. Mol. Neurobiol. 56, 2670–2684.
Coccurello, R., Castellano, C., Paggi, P., Mele, A., Oliverio, A., 2002. Genetically dystrophic *mdx/mdx* mice exhibit decreased response to nicotine in passive avoidance. Neuroreport 13, 1219–1222.
Comim, C.M., Cassol-Jr, O.J., Constantino, L.C., Constantino, L.S., Petronilho, F., Tuon, L., Vainzof, M., Dal-Pizzol, F., Quevedo, J., 2009a. Oxidative variables and antioxidant enzymes activities in the *mdx* mouse brain. Neurochem. Int. 55, 802–805.
Comim, C.M., Tuon, L., Stertz, L., Vainzof, M., Kapczinski, F., Quevedo, J., 2009b. Striatum brain-derived neurotrophic factor levels are decreased in dystrophin-deficient mice. Neurosci. Lett. 459, 66–68.

Comim, C.M., Moraz, T., Abreu, I., Fraga, D.B., Ghedim, F.V., Mildner, N., Tuon, L., Vainzof, M., Zugno, A.I., Quevedo, J., 2011. Reduction of acethylcolinesterase activity in the brain of *mdx* mice. Neuromuscul. Disord. 21, 359–362.
Comim, C.M., Hoepers, A., Ventura, L., Freiberger, V., Dominguini, D., Mina, F., Mendonça, B.P., Scaini, G., Vainzof, M., Streck, E.L., Quevedo, J., 2016. Activity of Krebs cycle enzymes in *mdx* mice. Muscle Nerve 53, 91–95.
Comim, C.M., Ventura, L., Freiberger, V., Dias, P., Bragagnolo, D., Dutra, M.L., Amaral, R.A., Camargo-Fagundes, A.L.S., Reis, P.A., Castro-Faria-Neto, H.C., Vainzof, M., Rosa, M.I., 2019. Neurocognitive impairment in *mdx* mice. Mol. Neurobiol. 56, n7608–n7616.
Connors, N.C., Adams, M.E., Froehner, S.C., Kofuji, P., 2004. The potassium channel Kir4.1 associates with the dystrophin-glycoprotein complex via α-Syntrophin in glia. J. Biol. Chem. 279, 28387–28392.
Cowan, L.D., Bodensteiner, J.B., Leviton, A., Doherty, L., 1989. Prevalence of epilepsies in children and adolescents. Epilepsia 30, 94–106.
Crisafulli, S., Sultana, J., Fontana, A., Salvo, F., Messina, S., Trifirò, G., 2020. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. Orphanet J. Rare Dis. 15, 141.
Cyrulnik, S.E., Hinton, V.J., 2008. Duchenne muscular dystrophy: a cerebellar disorder? Neurosci. Biobehav. Rev. 32, 486–496.
Cyrulnik, S.E., Fee, R.J., De Vivo, D.C., Goldstein, E., Hinton, V.J., 2007. Delayed developmental language milestones in children with Duchenne's muscular dystrophy. J. Pediatr. 150, 474–478.
Cyrulnik, S.E., Fee, R.J., Batchelder, A., Kiefel, J., Goldstein, E., Hinton, V.J., 2008. Cognitive and adaptive deficits in young children with Duchenne muscular dystrophy (DMD). J. Int. Neuropsychol. Soc. 14, 853–861.
Dallérac, G., Perronnet, C., Chagneau, C., Leblanc-Veyrac, P., Samson-Desvignes, N., Peltekian, E., Danos, O., Garcia, L., Laroche, S., Billard, J.-M., Vaillend, C., 2011. Rescue of a dystrophin-like protein by exon skipping normalizes synaptic plasticity in the hippocampus of the *mdx* mouse. Neurobiol. Dis. 43, 635–641.
Daoud, F., Angeard, N., Demerre, B., et al., 2009a. Analysis of Dp71 contribution in the severity of mental retardation through comparison of Duchenne and Becker patients differing by mutation consequences on Dp71 expression. Hum. Mol. Genet. 18, 3779–3794.
Daoud, F., Candelario-Martınez, A., Billard, J.-M., Avital, A., Khelfaoui, M., Rozenvald, Y., Guegan, M., Mornet, D., Jaillard, D., Nudel, U., Chelly, J., Martínez-Rojas, D., Laroche, S., Yaffe, D., Vaillend, C., 2009b. Role of mental retardation-associated dystrophin-gene product Dp71 in excitatory synapse organization, synaptic plasticity and behavioral functions. PLoS One 4 (8), e6574.
Darmahkasih, A.J., Rybalsky, I., Tian, C., Shellenbarger, K.C., Horn, P.S., Lambert, J.T., Wong, B.L., 2020. Neurodevelopmental, behavioral, and emotional symptoms common in Duchenne muscular dystrophy. Muscle Nerve 61, 466–474.
Davies, K.E., Nowak, K.J., 2006. Molecular mechanisms of muscular dystrophies: old and new players. Nat. Rev. Mol. Cell Biol. 7, 762–773.
de Brouwer, A.P., Nabuurs, S.B., Verhaart, I.E., Oudakker, A.R., Hordijk, R., Yntema, H. G., Hordijk-Hos, J.M., Voesenek, K., et al., 2014. A 3-base pair deletion, c.9711_9713del, in DMD results in intellectual disability without muscular dystrophy. Eur. J. Hum. Genet. 22, 480–485.
De Stefano, M.E., Zaccaria, M.L., Cavaldesi, M., Petrucci, T.C., Medori, R., Paggi, P., 1997. Dystrophin and its isoforms in a sympathetic ganglion of normal and dystrophic mdx mice: immunolocalization by electron microscopy and biochemical characterization. Neuroscience 80, 613–624.
De Stefano, M.E., Leone, L., Lombardi, L., Paggi, P., 2005. Lack of dystrophin leads to the selective loss of superior cervical ganglion neurons projecting to muscular targets in genetically dystrophic *mdx* mice. Neurobiol. Dis. 20, 929–942.
Del Signore, A., Gotti, C., De Stefano, M.E., Moretti, M., Paggi, P., 2002. Dystrophin stabilizes alpha 3- but not alpha 7-containing nicotinic acetylcholine receptor subtypes at the postsynaptic apparatus in the mouse superior cervical ganglion. Neurobiol. Dis. 10, 54–66.
Deng, B., Glanzma, D., Tidball, J.G., 2009. Nitric oxide generated by muscle corrects defects in hippocampal neurogenesis and neural differentiation caused by muscular dystrophy. J. Physiol. 587, 1769–1778.
Di Angelantonio, S., De Stefano, M.E., Piccioni, A., Lombardi, L., Gotti, C., Paggi, P., 2011. Lack of dystrophin functionally affects α3β2/β4-nicotinic acethylcholine receptors in sympathetic neurons of dystrophic *mdx* mice. Neurobiol. Dis. 41, 528–537.
Doorenweerd, N., 2020. Combining genetics, neuropsychology and neuroimaging to improve understanding of brain involvement in Duchenne muscular dystrophy - a narrative review. Neuromuscul. Disord. 30, 437–442.
Doorenweerd, N., Straathof, C.S., Dumas, E.M., Spitali, P., Ginjaar, I.B., Wokke, B.H., Schrans, D.G., van den Bergen, J.C., van Zwet, E.W., Webb, A., van Buchem, M.A., Verschuuren, J.J., Hendriksen, J.G., Niks, E.H., Kan, H.E., 2014. Reduced cerebral gray matter and altered white matter in boys with Duchenne Muscular Dystrophy. Ann. Neurol. 76, 403–411.
Doorenweerd, N., Mahfouz, A., van Putten, M., Kaliyaperumal, R., Pac, T.H., Hendriksen, J.G.M., Aartsma-Rus, A.M., Verschuuren, J.J.G.M., Niks, E.H., Reinders, M.J.T., Kan, H.E., Lelieveldt, B.P.F., 2017. Timing and localization of human dystrophin isoform expression provide insights into the cognitive phenotype of Duchenne muscular dystrophy. Sci. Rep. 7, 12575.
Dorman, C., Hurley, A.D., D'Avignon, J., 1988. Language and learning disorders of older boys with Duchenne muscular dystrophy. Dev. Med. Child Neurol. 30, 316–327.
Drenckhahn, D., Holbach, M., Ness, W., Schmitz, F., Anderson, L.V., 1996. Dystrophin and the dystrophin-associated glycoprotein, beta-dystroglycan, colocalize in photoreceptor synaptic complexes of the human retina. Neuroscience 73, 605–612.
Duan, D., Goemans, N., Takeda, S., Mercuri, E., Aartsma-Rus, A., 2021. Duchenne muscular dystrophy. Nat. Rev. Dis. Prim. 7.
Dubowitz, V., 1965. Intellectual impairment in muscular dystrophy. Arch. Dis. Child. 40, 296–301.
Dubowitz, V., 1978. Muscle disorders in childhood. Major Probl. Clin. Pediatr. 16, 1–282.
Dubowitz, V., 1979. Involvement of the nervous system in muscular dystrophies in man. Ann. N. Y. Acad. Sci. 317, 431–439.
Dubowitz, V., Crome, L., 1969. The central nervous system in Duchenne muscular dystrophy. Brain 92, 805–808.
Eid, T., Lee, T.S., Thomas, M.J., Amiry-Moghaddam, M., Bjørnsen, L.P., Spencer, D.D., Agre, P., Ottersen, O.P., de Lanerolle, N.C., 2005. Loss of perivascular aquaporin 4 may underlie deficient water and K^+ homeostasis in the human epileptogenic hippocampus. Proc. Natl. Acad. Sci. U. S. A. 102, 1193–1198.
Emery, A.E.H., 1993. Duchenne Muscular Dystrophy. In: Oxford Monographs on Medical Genetics, , (2nd ed.).xv. Oxford Univ. Press, Oxford, UK, p. 392.
Emery, A.E.H., 2002. The muscular dystrophies. Lancet 359, 687–695.
Emery, A.E.H., Skinner, R., 1976. Clinical studies in benign (Becker type) X-linked muscular dystrophy. Clin. Genet. 10, 189–201.
Ervasti, J.M., Ohlendieck, K., Kahl, S.D., Gaver, M.G., Campbell, K.P., 1990. Deficiency of a glycoprotein component of the dystrophin complex in dystrophic muscle. Nature 345, 315–319.
Etemadifar, M., Molaei, S., 2004. Epilepsy in boys with Duchenne Muscular Dystrophy. J. Res. Med. Sci. 3, 116–119.
Felisari, G., Martinelli Boneschi, F., Bardoni, A., Sironi, M., Comi, G.P., Robotti, M., Turconi, A.C., Lai, M., et al., 2000. Loss of Dp140 dystrophin. Isoform and intellectual impairment in Duchenne dystrophy. Neurology 55, 559–564.
Fitzgerald, K.M., Cibis, G.W., Giambrone, S.A., Harris, D.J., 1994. Retinal signal transmission in Duchenne muscular dystrophy: evidence for dysfunction in the photoreceptor/depolarizing bipolar cell pathway. J. Clin. Invest. 93, 2425–2430.
Fort, P.E., Sene, A., Pannicke, T., Roux, M.J., Forster, V., Mornet, D., Nudel, U., Yaffe, D., Reichenbach, A., Sahel, J.A., Rendon, A., 2008. Kir4.1 and AQP4 associate with Dp71- and Utrophin-DAPs complexes in specific and defined microdomains of Müller retinal glial cell membrane. Glia 56, 597–610.
Fradkin, L.G., Baines, R.A., van der Plas, M.C., Noordermeer, J.N., 2008. The dystrophin Dp186 isoform regulates neurotransmitter release at a central synapse in Drosophila. J. Neurosci. 28, 5105–5114.
Fragapane, P., Cosmi, F., De Stefano, M.E., 2020. Cultured hippocampal neurons of dystrophic *mdx* mice respond differently from those of wild typw mice to an acute treatment with corticosterone. Exp. Cell Res. 386, 111715.
Friedrich, O., von Wegner, F., Chamberlain, J.S., Fink, R.H.A., Rohrbach, P., 2008. L-Type Ca^{2+} Channel Function Is Linked to Dystrophin Expression in Mammalian Muscle. PlosOne 3, e1762.
Frigeri, A., Nicchia, G.P., Nico, B., Quondamatteo, F., Herken, R., Roncali, L., Svelto, M., 2001. Aquaporin-4 deficiency in skeletal muscle and brain of dystrophic *mdx* mice. FASEB J. 15, 90–98.
Fritschy, J.M., 2008. Epilepsy, E/I balance and GABA(A) receptor plasticity. Front. Mol. Neurosci. 28, 1–5.
Früh, S., Romanos, J., Panzanelli, P., Bürgisser, D., Tyagarajan, S.K., Campbell, K.P., Santello, M., Fritschy, J.-M., 2016. Neuronal Dystroglycan Is Necessary for Formation and Maintenance of Functional CCK-Positive Basket Cell Terminals on Pyramidal Cells. J. Neurosci. 36, 10296–10313.
Fuenzalida, M., Espinoza, C., Pérez, M.A., Tapia-Rojas, C., Cuitino, L., Brandan, E., Inestrosa, N.C., 2016. Wnt signaling pathway improves central inhibitory synaptic transmission in a mouse model of Duchenne muscular dystrophy. Neurobiol. Dis. 86, 109–120.
Fujimoto, T., Itoh, K., Yaoi, T., Fushiki, S., 2014. Somatodendritic and excitatory postsynaptic distribution of neuron-type dystrophin isoform, Dp40, in hippocampal neurons. Biochem. Biophys. Res. Commun. 452, 79–84.
Futai, K., Kim, M.J., Hashikawa, T., Scheiffele, P., Sheng, M., Hayashi, Y., 2007. Retrograde modulation of presynaptic release probability through signaling mediated by PSD-95-neuroligin. Nat. Neurosci. 10, 186–195.
García-Rodríguez, R., Hiller, M., Jiménez-Gracia, L., van der Pal, Z., Balog, J., Adamzek, K., Aartsma-Rus, A., Spitali, P., 2020. Premature termination codons in the DMD gene cause reduced local mRNA synthesis. Proc. Natl. Acad. Sci. U. S. A. 117, 16456–16464.
Ghedini, P.C., Avellar, M.C., De Lima, T.C., Lima-Landman, M.T., Lapa, A.J., Souccar, C., 2012. Quantitative changes of nicotinic receptors in the hippocampus of dystrophin deficient mice. Brain Res. 1483, 96–104.
Godfrey, C., Foley, A.R., Clement, E., Muntoni, F., 2011. Dystroglycanopathies: Coming into focus. Curr. Opin. Genet. Dev. 21, 278–285.
Goemans, N., Buyse, G., 2014. Current treatment and management of dystrophinopathies. Curr. Treat. Options Neurol. 16, 287.
Goodwin, F., Muntoni, F., Dubowitz, V., 1997. Epilepsy in Duchenne and Becker muscular dystrophies. Eur. J. Paediatr. Neurol. 4, 115–119.
Gosar, D., Kosmrlj, L., Musek, P.L., Mesko, T., Stropnik, S., Krkoc, V., Golli, T., Butenko, T., Loboda, T., Osredkar, D., 2021. Adaptive skills and mental health in children and adolescents with neuromuscular diseases. Eur. J. Paedr. Neurol. 30, P134–P143.
Gowers, W.R., 1879. Pseudo-hypertrophic muscular paralysis. J. & A. Churchill, London.
Goyenvalle, A., Griffith, G., Babbs, A., El Andaloussi, S., Ezzat, K., Avril, A., Dugovic, B., Chaussenot, R., Ferry, A., Voit, T., Amthor, H., Bühr, C., Schürch, S., Wood, M.J.A., Davies, K.E., Vaillend, C., Leumann, C., Garcia, L., 2015. Functional correction in mouse models of muscular dystrophy using exon-skipping tricyclo-DNA oligomers. Nat. Med. 21, 270–275.
Grain, L., Cortina-Borja, M., Forfar, C., Hilton-Jones, D., Hopkin, J., Burch, M., 2001. Cardiac abnormalities and skeletal muscle weakness in carriers of Duchenne and Becker muscular dystrophies and controls. Neuromuscul. Disord. 1, 186–191.

Guiraud, S., Aartsma-Rus, A., Vieira, N.M., Davies, K.E., van Ommen, G.J., Kunkel, L.M., 2015. The pathogenesis and therapy of muscular dystrophies. Annu. Rev. Genomics Hum. Genet. 16, 281–308.
Harriman, D.G.F., 1976. A comparison of the fine structure of motor end-plate in Duchenne dystrophy and in human neurogenic diseases. J. Neurol. Sci. 28, 233–247.
Hatten, M.E., 1999. Central nervous system neuronal migration. Annu. Rev. Neurosci. 22, 511–539.
Helleringer, R., Le Verger, D., Li, X., Izabelle, C., Chaussenot, R., Belmaati-Cherkaoui, M., Dammak, R., Decottignies, P., Daniel, H., Galante, M., Vaillend, C., 2018. Cerebellar synapse properties and cerebellum-dependent motor and non-motor performance in Dp71-null mice. Dis. Model. Mech. 11.
Hendriksen, R.G.F., Hoogland, G., Schipper, S., Hendriksen, J.G.M., Vles, J.S.H., Aalbers, M.W., 2015. A possible role of dystrophin in neuronal excitability: a review of the current literature. Neurosci. Biobehav. Rev. 51, 255–262.
Hendriksen, R.G.F., Vles, J.S.H., Aalbers, M.W., Chin, R.F.M., Hendriksen, J.G.M., 2018. Brain-related comorbidities in boys and men with Duchenne Muscular Dystrophy: A descriptive study. Eur. J. Peadr. Neurol. 22, 488–497.
Hinton, V.J., Nereo, N.E., Fee, R.J., Cyrulnik, S.E., 2006. Social behavior problems in boys with Duchenne muscular dystrophy. J. Dev. Behav. Pediatr. 27, 470–476.
Hinton, V.J., Cyrulnik, S.E., Fee, R.J., Batchelder, A., Kiefel, J.M., Goldstein, E.M., Kaufmann, P., De Vivo, D.C., 2009. Association of autistic spectrum disorders with dystrophinopathies. Pediatr. Neurol. 41, 339–346.
Hnia, K., Hugon, G., Masmoudi, A., Mercier, J., Rivier, F., Mornet, D., 2006. Effect of β-dystroglycan processing on utrophin/Dp116 anchorage in normal and *mdx* mouse Schwann cell membrane. Neuroscience 141, 607–620.
Hoffman, E.P., Brown Jr., R.H., Kunkel, L.M., 1987. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 51, 919–928.
Huard, J., Tremblay, J.P., 1992. Localization of dystrophin in the Purkinje cells of normal mice. Neurosci. Lett. 137, 105–108.
Iftikhar, M., Frey, J., Shohan, MdJ, Malek, S., Mousa, S.A., 2021. Current and emerging therapies for Duchenne muscular dystrophy and spinal muscular atrophy. Pharmacol. Therap. 220, 107719.
Im, W.B., Phelps, S.F., Copen, E.H., Adams, E.G., Slightom, J.L., Chamberlain, J.S., 1996. Differential expression of dystrophin isoforms in strains of i mice with different mutations. Hum. Mol. Genet. 5, 1149–1153.
Imamura, M., Araishi, K., Noguchi, S., Ozawa, E., 2000. A sarcoglycan-dystroglycam complex anchors Dp116 and utrophin in the peripheral nervous system. Hum. Mol. Genet. 9, 3091–3110.
Ishizaki, M., Kobayashi, M., Adachi, K., Matsumura, T., Kimura, E., 2018. Female dystrophinopathy: review of current literature. Neuromuscul. Disord. 28, 572–581.
Jagadha, V., Becker, L.E., 1988. Brain morphology in Duchenne muscular dystrophy: a Golgi study. Pediatr. Neurol. 4, 87–92.
Jastrow, H., Koulen, P., Altrock, W.D., Kröger, S., 2006. Identification of a beta-dystroglycan immunoreactive subcompartment in photoreceptor terminals. Invest. Ophthalmol. Vis. Sci. 47, 17–24.
Jennekens, F.G., Ten Kate, L.P., De Visser, M., Wintzen, A.R., 1991. Diagnostic criteria for Duchenne and Becker muscular dystrophy and myotonic dystrophy. Neuromuscul. Disord. 1, 389–391.
Jerusalem, F., Engel, A.G., Gomez, M.R., 1974. Duchenne dystrophy: II. Morphometric study of motor end-plate fine structure. Brain 97, 123–130.
Jung, D., Filliol, D., Metz-Boutigue, M.H., Rendon, A., 1993. Characterization and subcellular localization of the dystrophin-protein 71 (Dp71) from brain. Neuromuscul. Disord. 3, 515–518.
Karagan, N.J., Zellweger, H.U., 1978. Early verbal disability in children with Duchenne muscular dystrophy. Dev. Med. Child Neurol. 29, 435–441.
Karagan, N.J., Richman, L.C., Sorensen, J.P., 1980. Analysis of verbal disability in Duchenne muscular dystrophy. J. Nerv. Ment. Dis. 168, 419–423.
Kato, T., Nishina, M., Matsushita, K., Hori, E., Akaboshi, S., Takashima, S., 1997. Increased cerebral choline-compounds in Duchenne muscular dystrophy. Neuroreport 8, 1435–1437.
Kato, M., Das, S., Petras, K., Kitamura, K., Morohashi, K., Abuelo, D.N., Barr, M., Bonneau, D., Bradley, A.F., Carpenter, N.J., Cipero, K.N., Frisone, F., 2004. Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Hum. Mutat. 23, 147–159.
Khairallah, R.J., Shi, G., Sbrana, F., Prosser, B.J., Borrotto, C., Mazaitis, E.P., Hoffman, E. P., Mahurkar, A., Sachs, F., Sun, Y., Chen, Y.-W., Raiteri, R., Lederer, W.J., Dorsey, S. G., Ward, C., 2012. Microtubules underlie Dys function in Duchenne muscular dystrophy. Sci. Signal. 5 (ra56).
Kieny, P., Chollet, P., Delalande, P., Le Fort, M., Magot, A., Pereon, Y., Perrouin Verbe, B., 2013. Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. Ann. Phys. Rehabil. Med. 56, 443–454.
Kim, T.W., Wu, K., Xu, J.L., Back, I.B., 1992. Detection of dystrophin in the postsynaptic density of rat brain and deficiency in a mouse model of Duchenne muscular dystrophy. Proc. Natl. Acad. Sci. U. S. A. 89, 11642–11644.
Kim, T.W., Wu, K., Black, I.B., 1995. Deficiency of brain synaptic dystrophin in human Duchenne muscular dystrophy. Ann. Neurol. 38, 446–449.
Knuesel, I., Mastrocola, M., Zuellig, R.A., Bornhauser, B., Schaub, M.C., Fritschy, J.M., 1999. Altered synaptic clustering of GABAA receptors in mice lacking dystrophin (i mice). Eur. J. Neurosci. 11, 4457–4462.
Knuesel, I., Zuellig, R.A., Schaub, M.C., Fritschy, J.M., 2001. Alterations in dystrophin and utrophin expression parallel the reorganization of GABAergic synapses in a mouse model of temporal lobe epilepsy. Eur. J. Neurosci. 13, 1113–1124.
Koenig, M., Hoffman, E.P., Bertelson, C.J., Monaco, E.P., Feener, C., Kunkel, L.M., 1987. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell 50, 509–517.
Koenig, M., Monaco, E.P., Kunkel, L.M., 1988. The complete sequence of dystrophin predicts a rodshaped cytoskeletal protein. Cell 53, 219–226.
Kong, J., Anderson, J.E., 1999. Dystrophin is required for organizing large acetylcholine receptor aggregates. Brain Res. 839, 298–304.
Koulen, P., Blank, M., Kröger, S., 1998. Differential distribution of beta dystroglycan in rabbit and rat retina. J. Neurosci. Res. 51, 735–747.
Kozicka, A., Prot, J., Wasilewski, R., 1971. Mental retardation in patients with Duchenne progressive muscular dystrophy. J. Neurol. Sci. 14, 209–2013.
Krasowska, E., Zabłocki, K., Górecki, D.C., Swinny, J.D., 2014. Aberrant location of inhibitory synaptic marker proteins in the hippocampus of dystrophin-deficient mice: implications for cognitive impairment in Duchenne Muscular Dystrophy. PLoS One 9, e108364.
Kueh, S.L.L., Head, S.I., Morley, J.W., 2008. GABAA receptor expression and inhibitory post-synaptic inhibitory currents in cerebellar Purkinje cells in dystrophin deficient *mdx* mice. Clin. Exp. Pharmacol. Physiol. 35, 207–210.
Kueh, S.L.L., Dempster, J., Head, S.I., Morley, J.W., 2011. Reduced postsynaptic GABAA receptor number and enhanced gaboxadol induced change in holding currents in Purkinje cells of the dystrophin-deficient *mdx* mouse. Neurobiol. Dis. 43, 558–564.
Lederfein, D., Levy, Z., Augier, N., Mornet, D., Morris, G., Fuchs Yaffe, D., Nudel, U., 1992. A 71-kilodalton protein is a major product of the Duchenne muscular dystrophy gene in brain and other nonmuscle tissues. Proc. Natl. Acad. Sci. U. S. A. 89, 5346–5350.
Leibowitz, D., Dubowitz, V., 1981. Intellect and behaviour in Duchenne muscular dystrophy. Dev. Med. Child Neurol. 23, 577–590.
Lenk, U., Hanke, R., Thiele, H., Speer, A., 1993. A point mutation at the carboxy terminus of the human dystrophin gene: implication for an association with mental retardation in DMD patients. Hum. Mol. Genet. 2, 1877–1881.
Leyva-Leyva, M., Sandoval, A., Felix, R., González-Ramírez, R., 2018. Biochemical and functional interplay between ion channels and the components of the dystrophin-associated glycoprotein complex. J. Membr. Biol. 251, 535–550.
Licursi, V., Caiello, I., Lombardi, L., De Stefano, M.E., Negri, R., Paggi, P., 2012. Lack of dystrophin in *mdx* mice modulates the expression of genes involved in neuron survival and differentiation. Eur. J. Neurosci. 35, 691–701.
Lidov, H.G., Kunkel, L.M., 1998. Dystrophin and Dp140 in the adult rodent kidney. Lab. Investig. 78, 1543–1551.
Lidov, H.G.W., Byers, T.J., Watkins, S.C., Kunkel, L.M., 1990. Localization of dystrophin to postsynaptic regions of central nervous system cortical neurons. Nature 348, 725–728.
Lidov, H.G., Byers, T.J., Kunkel, L.M., 1993. The distribution of dystrophin in the murine central nervous system: an immunocytochemical study. Neuroscience 54, 167–187.
Lidov, H.G., Selig, S., Kunkel, L.M., 1995. Dp140: a novel 140 kDa CNS transcript from the dystrophin locus. Hum. Mol. Genet. 4, 329–335.
Lim, K.R.Q., Sheri, N., Nguyen, Q., Yokota, T., 2020. Cardiac involvement in dystrophin-deficient females: current understanding and implications for the treatment of dystrophinopathies. Genes 11, 765.
Lombardi, L., De Stefano, M.E., Paggi, P., 2008. Components of the NGF signaling complex are altered in mdx mouse superior cervical ganglion and its target organs. Neurobiol. Dis. 32, 402–411.
Lombardi, L., Persiconi, I., Gallo, A., De Stefano, Hoogenraad C.C., 2017. NGF-dependent axon growth and regeneration are altered in sympathetic neurons of dystrophic *mdx* mice. Mol. Cell. Neurosci. 80, 1–17.
Lopez, J.R., Kolster, J., Uryash, A., Estève, E., Altamirano, F., Adams, J.A., 2018. Dysregulation of intracellular Ca^{2+} in dystrophic cortical and hippocampal neurons. Mol. Neurobiol. 55, 603–618.
Lyons, P.R., Slater, C.R., 1991. Structure and function of the neuromuscular junction in young adult *mdx* mice. J. Neurocytol. 20, 969–981.
Mahyoob Rani, A.Q., Maeta, K., Kawaguchi, T., Awano, H., Nagai, M., Nishio, H., Matsuo, M., 2019. Schwann cell-specific Dp116 is expressed in glioblastoma cells, revealing two novel DMD gene splicing patterns. Byochem. Byophis. Rep. 20, 100703.
Marsh, G.G., Munsat, T.L., 1974. Evidence for early impairment of verbal intelligence in Duchenne muscular dystrophy. Arch. Dis. Child. 49, 118–122.
Matsuo, M., Awano, H., Matsumoto, M., Nagai, M., Kawaguchi, T., Zhang, Z., Nishio, H., 2017. Dystrophin Dp116: a yet to be investigated product of the Duchenne muscular dystrophy gene. Genes 8, 251.
McClure-Begley, T.D., King, N.M., Collins, A.C., Stitzel, J.A., Wehner, J.M., Butt, C.M., 2009. Acetylcholine-stimulated [3H]GABA release from mouse brain synaptosomes is modulated by alpha4beta2 and alpha4alpha5beta2 nicotinic receptor subtypes. Mol. Pharmacol. 75, 918–926.
Mehler, M.F., 2000. Brain dystrophin, neurogenetics and mental retardation. Brain Res. Rev. 32, 277–307.
Mehler, M.F., Haas, K.Z., Kessler, J.A., Stanton, P.K., et al., 1992. Enhanced sensitivity of hippocampal pyramidal neurons from mdx mice to hypoxia-induced loss of synaptic transmission. Proc. Nati. Acad. Sci. USA 89, 2461–2465. https://doi.org/10.1073/pnas.89.6.2461.
Mehler, M.F., Kessler, J.A., 1998. Neural progenitor cells and developmental disorders. Mental retardation and developmental disabilities. Res. Rev. 4, 143–149.
Melo, M., Vieira, A.H., Passos-Bueno, M.R., Zaty, M., 1993. Association of schizophrenia and Duchenne muscular dystrophy. Br. J. Psychiatry 162, 711–712.
Mendell, J.R., Shilling, C., Leslie, N.D., Flanigan, K.M., Al-Dahhak, R., Gastier-Foster, G., Kneile, K., Dunn, D.M., Duval, B., Aoyagi, A., Hamil, C., Mahmoud, M., Roush, K., Bird, L., Rankin, C., Lilly, H., Street, N., Chandrasekar, R., Weiss, R.B., 2012. Evidence-based path to newborn screening for Duchenne muscular dystrophy. Ann. Neurol. 71, 304–313.

Mercuri, E., Bonnemann, C.G., Muntoni, F., 2019. Muscular dystrophies. Lancet 394, 2025–2038.
Millay, D.P., Sargent, M.A., Osinska, H., Baines, C.P., Barton, E.R., Vuagniaux, G., Sweeney, H.L., Robbins, J., Molkentin, J.D., 2008. Genetic and pharmacologic inhibition of mitochondrial-dependent necrosis attenuates muscular dystrophy. Nat. Med. 14, 442–447.
Minatel, E., Santo Neto, H., Marques, M.J., 2003. Acetylcholine receptor distribution and synapse elimination at the developing neuromuscular junction of *mdx* mice. Muscle Nerve 28, 561–569.
Miranda, R., Sébrié, C., Degrouard, J., Gillet, B., Jaillard, D., Laroch, S., Vaillend, C., 2009. Reorganization of inhibitory synapses and increased PSD length of perforated excitatory synapses in hippocampal area CA1 of dystrophin-deficient *mdx* mice cerebral cortex, 19, pp. 876–888.
Miranda, R., Nudel, U., Laroche, S., Vaillend, C., 2011. Altered presynaptic ultrastructure in excitatory hippocampal synapses of mice lacking dystrophins Dp427 or Dp71. Neurobiol. Dis. 43, 134–142.
Miranda, R., Nagapin, F., Bozon, B., Laroche, S., Aubin, T., Vaillend, C., 2015. Altered social behavior and ultrasonic communication in the dystrophin deficient *mdx* mouse model of Duchenne muscular dystrophy. Mol. Autism 6, 60.
Miranda, R., Laroche, S., Vaillend, C., 2016. Reduced neuronal density in the CA1 anterodorsal hippocampus of the *mdx* mouse. Neuromuscul. Disord. 26, 775–781.
Morris, G.E., Simmons, C., Thi Man, N., 1995. Apodystrophins (Dp140 and Dp71)and dystrophin splicing isoforms in developing brain. Biochem. Biophys. Res. Commun. 215, 361–367.
Morrow, R.S., Cohen, J., 1954. The psychosocial factors in muscular dystrophy. J. Child Psychol. Psychiatry 3, 70–80.
Muntoni, F., Torelli, S., Ferlini, A., 2003. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. Lancet Neurol. 2, 731–740.
Murphy, E.G., Corey, P.N.J., Conen, P.E., 1964. Varying manifestations of Duchenne muscular dystrophy in a family with affected females. In: Paul, W.M., Daniel, E.E., Kay, C.M., Monckton, G. (Eds.), Muscle. Proceedings of symposium at faculty of Medicine. University of Alberta, New York, pp. 529–546. Pergamon Press.
Nagel, A., Lehmann-Horn, F., Engel, A.G., 1990. Neuromuscular transmission in the *mdx* mouse. Muscle Nerve 13, 742–749.
Nagelhus, E.A., Horio, Y., Inanobe, A., Fujita, A., Haug, F.M., Nielsen, S., Kurachi, Y., Ottersen, O.P., 1999. Immunogold evidence suggests that coupling of K1 siphoning and water transport in rat retinal Muller cells is mediated by a coenrichment of Kir4.1 and AQP4 in specific membrane domains. Glia 26, 47–54.
Naidoo, M., Anthony, K., 2020. Dystrophin Dp71 and the neuropathophysiology of Duchenne muscular dystrophy. Mol. Neurobiol. 57, 1748–1767.
Nakamura, A., 2015. X-Linked Dilated Cardiomyopathy: A Cardiospecific Phenotype of Dystrophinopathy. Pharmaceuticals 8, 303–320.
Nardes, F., Araujo, A.P., Ribeiro, M.G., 2012. Mental retardation in Duchenne muscular dystrophy. J. Pediatr. 88, 6–16.
Ng, S.Y., Ljubicic, V., 2020. Recent insights into neuromuscular junction biology in Duchenne muscular dystrophy: Impacts, challenges, and opportunities. EBioMedicine 61, 103032.
Nicchia, G.P., Nico, A.B., Camassa, B.L.M.A., Mola, A.M.G., Loh, A.N., Dermietzel, C.R., Spray, D.D.C., Sveltoa, E.M., Frigeri, A., 2004. The role of aquaporin-4 in the blood–brain barrier development and integrity: studies in animal and cell culture models. Neuroscience 129, 935–945.
Ohlendieck, K., Swandulla, D., 2021. Complexity of skeletal muscle degeneration: multi-systemspatho physiology and organ crosstalk in dystrophinopathy. Pflugers Arch. https://doi.org/10.1007/s00424-021-02623-1.
Omori, Y., Araki, F., Chaya, T., Kajimura, N., Irie, S., Terada, K., Muranishi, Y., Tsujii, T., Ueno, S., Koyasu, T., Tamaki, Y., Kondo, M., Amano, S., Furukawa, T., 2012a. Presynaptic dystroglycan-pikachurin complex regulates the proper synaptic connection between retinal photoreceptor and bipolar cells. J. Neurosci. 32, 6126–6137.
Omori, Y., Araki, F., Chaya, T., Kajimura, N., Irie, S., Terada, K., Muranishi, Y., Tsujii, T., Ueno, S., Koyasu, T., Tamaki, Y., Kondo, M., Amano, S., Furukawa, T., 2012b. Presynaptic dystroglycan-pikachurin complex regulates the proper synaptic connection between retinal photoreceptor and bipolar cells. J. Neurosci. 32, 6126–6137.
Pane, M., Lombardo, M.E., Alfieri, P., D'Amico, A., Bianco, F., Vasco, G., Piccini, G., Mallardi, M., Romeo, D.M., Ricotti, V., Ferlini, A., Gualandi, F., Vicari, S., Bertini, E., Berardinelli, A., Mercuri, E., 2012. Attention deficit hyperactivity disorder and cognitive function in Duchenne muscular dystrophy: phenotype-genotype correlation. J. Pediatr. 161, 705–709.
Pane, M., Scalise, R., Berardinelli, A., D'Angelo, G., Ricotti, V., Alfieri, P., Moroni, I., Hartley, L., Pera, M.C., Baranello, G., Catteruccia, M., Casalino, T., Romeo, D.M., Graziano, A., Gandioli, C., Bianco, F., Mazzone, E.S., Lombardo, M.E., Scoto, M., Sivo, S., Palermo, C., Gualandi, F., Sormani, M.P., Ferlini, A., Bertini, E., Muntoni, F., Mercuri, E., 2013. Early neurodevelopmental assessment in Duchenne muscular dystrophy. Neuromuscul. Disord. 23, 451–453.
Parisi, L., Di Filippo, T., Glorioso, P., La Grutta, S., Epifanio, M.S., Roccella, M., 2018. Autism spectrum disorders in children affected by Duchenne muscular dystrophy. Minerva Pediatr. 70, 233–239.
Peña-Padilla, C., Romero-Valenzuela, I., Baldomero-López, A., Sandoval-Talamantes, A. K., Castellanos-González, A., Nagy, P.L., Kelly, R.R., Corona-Rivera, J., 2021. Third case of Duchenne muscular dystrophy and West syndrome: Expanding the spectrum of the DMD neuropsychiatric phenotype. Neuromuscul. Disord. 31, 462–465.
Pereira da Silva, J.D., Vannucci Campos, D., Nogueira-Bechara, M., Sessa Stilhano, R., Won Han, S., Sinigaglia-Coimbra, R., Lima-Landman, M.T.R., Lapa, A.J., Souccar, C., 2018. Altered release and uptake of gamma-aminobutyric acid in the cerebellum of dystrophin-deficient mice. Neurochem. Int. 118, 105–114.
Perronnet, C., Vaillend, C., 2010. Dystrophins, utrophins, and associated scaffolding complexes: role in mammalian brain and implications for therapeutic strategies. J. Biomed. Biotechnol. 2010, 849426.
Persiconi, I., Cosmi, F., Guadagno, N.A., Lupo, G., De Stefano, M.E., 2020. Dystrophin is required for the proper timing in retinal histogenesis: a thorough investigation on the *mdx* mouse model of Duchenne muscular dystrophy. Front. Neurosci. 14, 760.
Piccini, G., Gazzellini, S., D'Amico, A., Pane, M., Castelli, E., Vicari, S., 2014. Developmental lag of visuospatial attention in Duchenne muscular dystrophy. Res. Dev. Disabil. 14, 55–61.
Pilgram, G.S.K., Potikanond, S., Baines, R.A., Fradkin, L.G., Noordermeer, J.N., 2010. The Roles of the Dystrophin-associated glycoprotein complex at the synapse. Mol. Neurobiol. 41, 1–21.
Pratt, S.J.P., Valencia, A.P., Le, G.K., Shah, S.B., Lovering, R.M., 2015. Pre- and postsynaptic changes in the neuromuscualr junction in dystrophic mice. Front. Physiol. 6, 252.
Preethish-Kumar, V., Shah, A., Kumar, M., Ingalhalikar, M., Polavarapu, K., Afsar, M., Rajeswaran, J., Vengalil, S., Nashi, S., Thomas, P.T., Sadasivan, A., Warrier, M., Nalini, A., Saini, J., 2020. *In vivo* evaluation of white matter abnormalities in children with Duchenne muscular dystrophy using DTI. AJNR Am. J. Neuroradiol. 41, 1271–1278.
Pribiag, H., Peng, H., Shah, W.A., Stellwagen, D., Carbonetto, S., 2014. Dystroglycan mediates homeostatic synaptic plasticity at GABAergic synapses. Proc. Natl. Acad. Sci. U. S. A. 111, 6810–6815.
Prins, K.W., Humston, J.L., Mehta, A., Tate, V., Ralston, E., Ervasti, J.M., 2009. Dystrophin is a microtubule-associated protein. J. Cell Biol. 186, 363–369.
Prosser, E.J., Murphy, E.G., Thompson, M.W., 1969. Intelligence and the gene for Duchenne muscular dystrophy. Arch. Dis. Child. 44, 221–230.
Prosser, B.L., Ward, C.W., Lederer, W.J., 2011. X-ROS signaling: rapid mechano-chemo transduction in heart. Science 333, 1440–1445.
Rae, M.G., O'Malley, D., 2016. Cognitive dysfunction in Duchenne muscular dystrophy: a possible role for neuromodulatory immune molecules. J. Neurophysiol. 116, 1304–1315.
Rae, C., Scott, R.B., Thompson, C.H., Dixon, R.M., Dumughn, I., Kemp, G.J., Male, A., Pike, M., Styles, P., Radda, G.K., 1998. Brain biochemistry in Duchenne muscular dystrophy; a 1H magnetic resonance and neuropsychological study. J. Neurol. Sci. 160, 148–157.
Rae, C., Griffina, J.L., Blair, D.H., Bothwell, J.H., Bubb, W.A., Maitland, A., Head, S., 2002. Abnormalities in brain biochemistry associated with lack of dystrophin: studies of the *mdx* mouse. Neuromuscul. Disord. 12, 121–129.
Razzoli, M., Lindsay, A., Law, M.L., Chamberlain, C.M., Southern, W.M., Berg, M., Osborn, J., Engeland, W.C., Metzger, J.M., Ervasti, J.M., Bartolomucci, A., 2020. Social stress is lethal in the *mdx* model of Duchenne muscular dystrophy. EBioMedicine 55, 102700. http://creativecommons.org/licenses/by-nc-nd/4.0/.
Reinig, A.M., Mirzaei, S., Berlau, D.J., 2017. Advances in the Treatment of Duchenne Muscular Dystrophy: New and Emerging Pharmacotherapies. Pharmacotherapy 37, 492–499.
Ricotti, V., Muntoni, F., Voit, T., 2015. Challenges of clinical trial design for DMD. Neuromuscul. Disord. 12, 932–935.
Ricotti, V., Mandy, W.P.L., Scoto, M.C., Pane, M., Deconinck, N., Messina, S., Mercuri, E., Skuse, D.H., Muntoni, F., 2016. Neurodevelopmental, emotional, and behavioural problems in Duchenne muscular dystrophy in relation to underlying dystrophin gene mutations. Dev. Med. Child Neurol. 58, 77–84.
Robinow, M., 1976. Mental retardation in Duchenne Muscular dystrophy: its relation to the maternal carrier state. J. Pediatr. 188, 896–897.
Romo-Yáñez, J., Rodríguez-Martínez, G., Aragón, J., Siqueiros-Márquez, L., Herrera-Salazar, A., Velasco, I., Montanez, C., 2020. Characterization of the expression of dystrophins and dystrophin associated proteins during embryonic neural stem/progenitor cell differentiation. Neurosci. Lett. 736, 135247.
Rosman, N.P., Kakulas, B.A., 1966. Mental deficiency associated with muscular dystrophy: A neuropathological study. Brain 89, 769–788.
Rubi, L., Koenig, X., Kubista, H., Todt, H., Hilber, K., 2017. Decreased inward rectifier potassium current IK1 in dystrophin-deficient ventricular cardiomyocytes. Channels (Austin, Tex.) 11, 101–108.
Ryder, S., Leadley, R.M., Armstrong, N., Westwood, M., de Kock, S., Butt, T., Jain, M., Kleijnen, J., 2017. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. Orphanet J. Rare Dis. 12, 79.
Sabourin, J., Lamiche, C., Vandebrouck, A., Magaud, C., Rivet, J., Cognard, C., Bourmeyster, N., Constantin, B., 2009. Regulation of TRPC1 and TRPC4 cation channels requires an alpha1-syntrophin-dependent complex in skeletal mouse myotubes. J. Biol. Chem. 284, 36248–36261.
Sadoulet-Puccio, H.M., Kunkel, L.M., 1996. Dystrophin and its isoforms. Brain Pathol. 6, 25–35.
Sakakibara, H., Engel, A.G., Lambert, E.H., 1977. Duchenne dystrophy: ultrastructural localization of the acetylcholine receptor and intracellular microelectrode studies of neuromuscular transmission. Neurology 27, 741–745.
Sakamoto, T., Arima, T., Ishizaki, M., Kawano, R., Koide, T., Uchida, Y., Yamashita, S., Kimura, E., Hirano, T., Maeda, Y., Uchino, M., 2008. Regions downstream from the WW domain of dystrophin are important for binding to postsynaptic densities in the brain. Neuromuscul. Disord. 18, 382–388.
Sander, M., Chavoshan, B., Iannaccone, Harris S.A., Stull, J.T., Thomas, J.D., Victor, R. G., 2000. Functional muscle ischemia in neuronal nitric oxide synthase-deficient skeletal muscle of children with Duchenne muscular dystrophy. Proc. Natl. Acad. Sci. U. S. A. 97, 13818–13823.
Saoudi, A., Zarrouki, F., Sebrié, C., Izabelle, C., Goyenvalle, A., Vaillend, C., 2021. Emotional behavior and brain anatomy of the *mdx52* mouse model of Duchenne muscular dystrophy. Dis. Model. Mech. 14, dmm049028.

Sato, S., Omori, Y., Katoh, K., Kondo, M., Kanagawa, M., Miyata, K., Funabiki, K., Koyasu, T., Kajimura, N., Miyoshi, T., Sawai, H., Kobayashi, K., Tani, A., Toda, T., Usukura, J., Tano, Y., Fujikado, T., Furukawa, T., 2008. Pikachurin, a dystroglycan ligand, is essential for photoreceptor ribbon synapse formation. Nat. Neurosci. 11, 923–931.

Sbriccoli, A., Santarelli, M., Carretta, D., Pinto, F., Granato, A., Minciacchi, D., 1995. Architectural changes of the cortico-spinal system in the dystrophin defective *mdx* mouse. Neurosci. Lett. 200, 53–56.

Schmitz, F., Drenckhahn, D., 1997. Localization of dystrophin and beta dystroglycan in bovine retinal photoreceptor processes extending into the postsynaptic dendritic complex. Histochem. Cell Biol. 108, 249–255.

Schoelly, M.L., Fraser, A.W., 1955. Emotional reactions in muscular dystrophy. Am. J. Phys. Med. 34, 119–123.

Sekiguchi, M., Zushida, K., Yoshida, M., Maekawa, M., Kamichi, S., Yoshida, M., SaharaY, Yuasa S., Takeda, S., Wada, K., 2009. A deficit of brain dystrophin impairs specific amygdala GABAergic transmission and enhances defensive behaviour in mice. Brain 132, 124–135.

Sesay, A.K., Errington, M.L., Levita, L., Bliss, T.V., 1996. Spatial learning and hippocampal long-term potentiation are not impaired in *mdx* mice. Neurosci. Lett. 211, 207–210.

Shiga, K., Yoshioka, H., Matsumiya, T., Kimura, I., Takeda, S., Imamura, M., 2006. Zeta-sarcoglycan is a functional homologue of gamma-sarcoglycan in the formation of the sarcoglycan complex. Exp. Cell Res. 312, 2083–2092.

Snow, W.M., Anderson, J.E., Jakobson, L.S., 2013. Neuropsychological and neurobehavioral functioning in Duchenne muscular dystrophy: a review. Neurosci. Biobehav. Rev. 37, 743–752.

Sollee, N.D., Latham, E.E., Kindlon, D.J., Bfesnan, M.J., 1985. Neuropsychological impairment in Duchenne muscular dystrophy. J. Clin. Exp. Neuropsychol. 7, 486–496.

Stockton, R.A., Slaughter, M.M., 1989. B-wave of the electroretinogram. A reflection of ON bipolar cell activity. J. Gen. Physiol. 93, 101–122.

Strehle, E.M., Straub, V., 2015. Recent advances in the management of Duchenne muscular dystrophy. Arch. Dis. Child. 100, 1173–1177.

Sugita, S., Saito, F., Tang, J., Satz, J., Campbell, K., Südhof, T.C., 2001. A stoichiometric complex of neurexins and dystroglycan in brain. J. Cell Biol. 154, 435–445.

Tadayoni, R., Rendon, A., Soria-Jasso, L.E., Cisneros, B., 2012. Dystrophin Dp71: the smallest but multifunctional product of the Duchenne muscular dystrophy gene. Mol. Neurobiol. 45, 43–60.

Thangarajh, M., Elfring, G.L., Trifillis, P., 2020. Longitudinal evaluation of working memory in Duchenne muscular dystrophy. J. Clin. Med. 9, 2940.

Tinsley, J.M., Blake, D.J., Davies, K.E., 1993. Apo-dystrophin-3: a 2.2 kb transcript from the DMD locus encoding the dystrophin glycoprotein binding site. Hum. Mol. Genet. 2, 521.524.

Tozawa, T., Itoh, K., Yaoi, T., Tando, S., Umekage, M., Dai, H., Hosoi, H., Fushiki, S., 2012. The shortest isoform of dystrophin (Dp40) interacts with a group of presynaptic proteins to form a presumptive novel complex in the mouse brain. Mol. Neurobiol. 45, 287–297.

Tracey, I., Scott, R.B., Thompson, C.H., Dunn, J.F., Barnes, P.R., Styles, P., Kemp, G.J., Rae, C.D., Pike, M., Radda, G.K., 1995. Brain abnormalities in Duchenne muscular dystrophy: phosphorus-31 magnetic resonance spectroscopy and neuropsychological study. Lancet 345, 1260–1264.

Truitt, C.L., 1955. Personal and social adjustment of children with muscular dystrophy. Am. J. Phys. Med. 34, 124–128.

Tuon, L., Comim, C.M., Fraga, D.B., Scaini, G., Rezin, G.T., Baptista, B.R., Streck, E.L., Vainzof, M., Quevedo, J., 2010. Mitochondrial respiratory chain and creatine kinase activities in mdx mouse brain. Muscle Nerve 41, 257–260.

Turner, P.R., Westwood, T., Regen, C.M., Steinhardt, R.A., 1988. Increased protein degradation results from elevated free calcium levels found in muscle from *mdx* mice. Nature 335, 735–738.

Turrigiano, G., 2012. Homeostatic synaptic plasticity: Local and global mechanisms for stabilizing neuronal function. Cold Spring Harb. Perspect. Biol. 4, a005736.

Tyagi, R., Aggarwal, P., Mohanty, M., Dutt, V., Anand, A., 2020. Computational cognitive modeling and validation of Dp140 induced alteration of working memory in Duchenne Muscular Dystrophy. Sci. Rep. 10, 11989.

Uchino, M., Teramoto, H., Naoe, H., Miike, T., Yoshioka, K., Ando, M., 1994a. Dystrophin and dystrophin-related protein in the central nervous system of normal controls and Duchenne muscular dystrophy. Acta Neuropathol. 87, 129–134.

Uchino, M., Teramoto, H., Naoe, H., Yoshioka, K., Miike, T., Ando, M., 1994b. Localisation and characterisation of dystrophin in the central nervous system of controls and patients with Duchenne muscular dystrophy. J. Neurol. Neurosurg. Psychiatry 57, 426–429.

Ueda, H., Baba, T., Terada, N., Kato, Y., Tsukahara, S., Ohno, S., 1997a. Dystrophin in rod spherules; submembranous dense regions facing bipolar cell processes. Histochem. Cell Biol. 108, 243–248.

Ueda, H., Kato, Y., Baba, T., Terada, N., Fujii, Y., Tsukahara, S., Ohno, S., 1997b. Immunocytochemical study of dystrophin localization in cone cells of mouse retinas. Invest. Ophthalmol. Vis. Sci. 38, 1627–1630.

Ueda, H., Baba, T., Ohno, S., 2000. Current knowledge of dystrophin and dystrophin-associated proteins in the retina. Histol. Histopathol. 15, 753–760.

Uezu, A., Hisey, E., Kobayashi, Y., Gao, Y., Bradshaw, T.W.A., Devlin, P., Rodriguiz, R., Tata, P.R., Soderling, S., 2019. Essential role for InSyn1 in dystroglycan complex integrity and cognitive behaviors in mice. eLife 8, e50712.

Vaillend, C., Billard, J.-M., 2002. Facilitated CA1 hippocampal synaptic plasticity in dystrophin-deficient mice: Role for GABAA Receptors? Hippocampus 12, 713–717.

Vaillend, C., Chaussenot, R., 2017. Relationships linking emotional, motor, cognitive and GABAergic dysfunctions in dystrophin-deficient *mdx* mice. Hum. Mol. Genet. 26, 1041–1055.

Vaillend, C., Billard, J.-M., Dutar, P., Claudepierre, T., Rendon, A., Ungerer, A., 1998. Spatial discrimination learning and CA1 hippocampal synaptic plasticity in *mdx* and *mdx3cv* mice lacking dystrophin-brain isoforms. Neuroscience 86, 53–66.

Vaillend, C., Billard, J.M., Claudepierre, T., Rendon, A., Dutar, P., Ungerer, A., 1999a. Spatial discrimination learning and CA1 hippocampal synaptic plasticity in *mdx* and *mdx*^{3cv} mice lacking dystrophin gene products. Neuroscience 86, 53–66.

Vaillend, C., Ungerer, A., Billard, J.M., 1999b. Facilitated NMDA receptor mediated synaptic plasticity in the hippocampal CA1 area of dystrophin-deficient mice. Synapse 33, 59–70.

Vaillend, C., Rampon, C., Davis, S., Laroche, S., 2002. Gene control of synaptic plasticity and memory formation: implications for diseases and therapeutic strategies. Curr. Mol. Med. 2, 613–628.

Vaillend, C., Billard, J.-M., Laroche, S., 2004. Impaired long-term spatial and recognition memory and enhanced CA1 hippocampal LTP in the dystrophin deficient *Dmdmdx* mouse. Neurobiol. Dis. 17, 10–20.

Vaillend, C., Perronnet, C., Ros, C., Gruszczynski, C., Goyenvalle, A., Laroche, S., Danos, O., Garcia, L., Peltekian, E., 2010. Rescue of a dystrophin-like protein by exon skipping in vivo restores GABAA-receptor clustering in the hippocampus of the *mdx* mouse. Mol. Ther. 18, 1683–1688.

van der Pijl, E.M., van Putten, M., Niks, E.H., Vershuuren, J.J.G.M., Aartsma-Rus, A., Plomp, J.J., 2016. Characterization of neuromuscular synapse function abnormalities in multiple Duchenne muscular dystrophy mouse models. Eur. J. Neurosci. 43, 1623–1635.

van der Pijl, E.M., van Putten, M., Niks, E.H., Vershuuren, J.J.G.M., Aartsma-Rus, A., Plomp, J.J., 2018. Low dystrophin levels and insufficient to normalize the neuromuscular synaptic abnormalities of *mdx* mice. Neuromuscul. Disord. 28, 427–442.

van der Plas, M.C., Pilgram, G.S., Plomp, J.J., de Jong, A., Fradkin, L.G., Noordermeer, J. N., 2006. Dystrophin is required for appropriate retrograde control of neurotransmitter release at the Drosophila neuromuscular junction. J. Neurosci. 26, 333–344.

Varoqueaux, F., Jamain, S., Brose, N., 2004. Neuroligin 2 is exclusively localized to inhibitory synapses. Eur. J. Cell Biol. 83, 449–456.

Vignos Jr., P.J., 1977. Intellectual function and educational achievements in Duchenne muscular dystrophy. Isr. J. Med. Sci. 13, 215–222.

Wairkar, Y.P., Fradkin, L.G., Noordermeer, J.N., DiAntonio, A., 2008. Synaptic defects in a *Drosophila* model of congenital muscular dystrophy. J. Neurosci. 28, 3781–3789.

Waite, A., Tinsley, C.L., Locke, M., Blake, D.J., 2009. The neurobiology of the dystrophin-associated glycoprotein complex. Ann. Med. 41, 344–359.

Wallis, T., Bubb, W.A., McQuillan, J.A., Balcar, V.J., Rae, C., 2004. For want of a nail. ramifications of a single gene deletion, dystrophin, in the brain of the mouse. Front. Biosci. 9, 74–84.

Walton, J.N., Nattrass, Fl, 1954. On the classification, natural history and treatment of myopathies. Brain 77, 169–231.

Wersinger, E., Bordais, A., Schwab, Y., Sene, A., Bénard Alunni, V., Sabel, J.A., Rendon, A., Roux, M.J., 2011. Reevaluation of dystrophin localization in the mouse retina. Invest. Ophthalmol. Vis. Sci. 52, 7901–7908.

Willis, B.C., Ponce-Balbuena, D., Jalife, J., 2015. Protein assemblies of sodium and inward rectifier potassium channels control cardiac excitability and arrhythmogenesis. Am. J. Physiol. Heart Circ. Physiol. 308, H1463–H1473.

Willmann, R., Possekel, S., Dubach-Powell, J., Meier, T., Ruegg, M.A., 2009. Mammalian animal models for Duchenne muscular dystrophy. Neuromuscul. Disord. 19, 241–249.

Wood, S.J., Slater, C.R., 1998. Beta-spectrin is colocalized with both voltage-gated sodium channels and ankyrinG at the adult rat neuromuscular junction. J. Cell Biol. 140, 675–684.

Worden, D.K., Vignos Jr., P.J., 1962. Intellectual function in childhood progressive muscular dystrophy. Pediatrics 29, 968–977.

Yang, B., Jung, D., Motto, D., Meyer, J., Koretzky, G., Campbell, K.P., 1995. SH3 domain-mediated interaction of dystroglycan and Grb2. J. Biol. Chem. 270, 11711–11714.

Zaccaria, M.L., De Stefano, M.E., Properzi, F., Gotti, C., Petrucci, T.C., Paggi, P., 1998. Disassembly of the cholinergic postsynaptic apparatus induced by axotomy in mouse sympathetic neurons: loss of dystrophin and β-dystroglycan immunoreactivity precedes that of the acetylcholine receptor. J. Neuropathol. Exp. Neurol. 57, 768–779.

Zaccaria, M.L., De Stefano, M.E., Gotti, C., Petrucci, T.C., Paggi, P., 2000. Selective reduction in the nicotinic acetylcholine receptor and dystroglycan at the postsynaptic apparatus of *mdx* mouse superior cervical ganglion. J. Neuropathol. Exp. Neurol. 59, 103–112.

Zappettini, S., Grilli, M., Lagomarsino, F., Cavallero, A., Fedele, E., Marchi, M., 2011. Presynaptic nicotinic alpha7 and non-alpha7 receptors stimulate endogenous GABA release from rat hippocampal synaptosomes through two mechanisms of action. PLoS One 6, e16911.

Zatz, M., Vallada, H., Melo, M.S., Passon-Bueno, M.R., Vieira, A.H.G., Vainzof, M., Gill, M., Gentil, V., 1993. Cosegregation of schizophrenia with Becker muscular dystrophy: susceptibility locus for schizophrenia at Xp21 or an effect of the dystrophin gene in the brain? J. Med. Genet. 30, 131–134.

Zellweger, H., Hanson, J.W., 1967. Psychometric studies in muscular dystrophy type Illa (Duchenne). Dev. Med. Child Neurol. 9, 576–581.
Zellweger, H., Niedermeyer, E., 1965. Central nervous system manifestation s in childhood muscular dystrophy (CMD), 1. Psychometric and electroencephalographic findings. Ann. Pediatr. 205, 25–42.
Zimprich, A., Grabowski, M., Asmus, F., Naumann, M., Berg, D., Bertram, M., Scheidtmann, K., Kern, P., Winkelmann, J., Müller-Myhsok, B., Riedel, L., Bauer, M., Müller, T., Castro, M., Meitinger, T., Strom, T.M., Gasser, T., 2001. Mutations in the gene encoding epsilon sarcoglycan cause myoclonus-dystonia syndrome. Nat. Genet. 29, 66–69.