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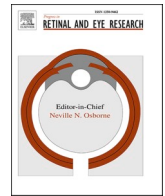
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## Retinal dystrophins and the retinopathy of Duchenne muscular dystrophy

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## ABSTRACT

Duchenne muscular dystrophy (DMD) is caused by X-linked inherited or *de novo* DMD gene mutations predominantly affecting males who develop early-onset muscle degeneration, severely affecting their quality of life and leading to reduced life expectancy. DMD patients may also develop proliferative retinopathy, cataract, ERG abnormalities, altered contrast sensitivity, color vision losses, and elevated flash detection thresholds during dark adaptation. Depending on the position of the genetic alteration in the large DMD gene, it is associated with a lack of the full-length dystrophin protein possibly with an additional loss of one or several other dystrophins, which are normally transcribed from internal promoters in retina and crystalline lens. During the last decades, the properties of the dystrophins have been characterized in patients with different genetic alterations and in genetic mouse models of DMD. The complex expression pattern of the dystrophins in photoreceptors, Müller glial cells and astrocytes, likely influences synaptic transmission, ionic balance and vascular integrity of the retina. However, the specific function of each retinal dystrophin remains largely unknown. This review describes the current knowledge on dystrophin expression, the putative molecular, structural, and physiological properties of retinal dystrophins, and the main clinical implications associated with the loss of dystrophins in DMD patients and mouse models. Current data and working hypotheses warrant future research on retinal dystrophins to increase our understanding of dystrophin function in the central nervous system in general and to unveil new retinal mechanisms and therapeutic avenues for retinal diseases.

## 1. Introduction

Dystrophinopathies are X-linked recessive muscular dystrophies caused by genetic mutations in the dystrophin gene (DMD MIM:

300377), which result in dysfunctional dystrophin proteins. Dystrophinopathies include Duchenne muscular dystrophy (DMD; MIM: 310200) and Becker muscular dystrophy (BMD; MIM: 300376), which are associated with a variable spectrum of clinical features and severity

**Abbreviations:** DMD, Duchenne Muscular Dystrophy; BMD, Becker Muscular Dystrophy; Dp, Dystrophin protein; DAP, Dystrophin-associated protein; DGC, dystrophin-associated glycoprotein complex; MGC, Müller glial cell; AQP4, aquaporin-4; CICR, calcium-induced calcium release; ONL, outer nuclear layer; OPL, outer plexiform layer; GCL, ganglion cell layer; CSNB, congenital stationary night blindness; CCT, Cambridge Color Test; ISCEV, International Society for Clinical Electrophysiology of Vision; OPs, oscillatory potentials; VEGF, vascular endothelial growth factor.

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depending on the position of the genetic alteration within the *DMD* gene (O'Brien and Kunkel, 2001). DMD is the most prevalent dystrophinopathy affecting approximately one in 5000 live births (Crisafulli et al., 2020). The symptoms are detected from the beginning of childhood and they rapidly progress. BMD is a less common condition that results in milder symptoms with disease onset usually at older ages and slower progression compared to DMD (Emery, 1998). Clinical cases of DMD/BMD have been reported since the eighteenth century, but it was only in the 1860s that the French neurologist Guillaume Benjamin Amand Duchenne de Boulogne (1806–1875) detailed muscle histology, clinical features and clinical progression of this disease (Duchenne, 1868) that has been later associated with his name (Emery and Emery, 1993; Jay and Vajsar, 2001). Duchenne also pointed for the first time to the presence of comorbidities in the central nervous system, which have been later shown to be independent from their motor handicap (e.g., Billard et al., 1992). Walton and Nattrass (1954) defined muscular dystrophies as diseases of hereditary origin, characterized by progressive atrophy and muscle weakness associated with the degeneration and necrosis of muscle fibers, increase in connective tissue, and fat infiltration of muscle tissues. In the late 1980's, the X chromosome-linked (Xp21) *DMD* gene mutations were finally reported to be the cause of these muscular dystrophies (Koenig et al., 1987).

The complex genomic organization of the *DMD* gene causes the expression of a diversity of dystrophins produced by several (internal) promoters (Muntoni et al., 2003) also in the central nervous system (Lidov et al., 1990; Wersinger et al., 2011). This underlies the well-established association between *DMD* gene mutations and the presence of cognitive (Bresolin et al., 1994) and retinal (Cibis et al., 1993) comorbidities. Although several studies have addressed selective retinal alterations during the last 30 years, the functional links between the lack of specific dystrophins and visual functions remain to be further detailed to open new routes for therapeutic intervention based on the rescue of each retinal dystrophin. Pioneer investigations (Cibis et al., 1993; Fitzgerald et al., 1994; Pillers et al., 1993) pointed to non-linear/non-predictable associations between dystrophin expression and function of the retina. In addition, the repercussions of retinal abnormalities on visual capacities of DMD patients is not well understood. Even though visual symptoms in DMD patients are known, they are less well studied probably because other symptoms are far more restrictive. While stationary ophthalmological symptoms, such as the negative dark-adapted electroretinogram, are highly prevalent in DMD patients (Sigesmund et al., 1994), other severe ocular alterations such as neovascularization and fibrovascular changes in the retina may be triggered by age (Bucher et al., 2019). Therefore, the improved life expectancy provided by the clinical application of emerging therapies in DMD patients may influence the incidence of moderate to severe retinopathy.

The present review aims to describe the current knowledge on the putative roles of dystrophins in the retina, how retinal structure and function are affected by dystrophinopathies, and what could be the prospects and challenges for therapeutic strategies. Data from non-mammals, such as *Drosophila* and fishes and from sporadically used mammalian models are described to highlight their utility in specific structure-function studies. However, we concentrated upon patient data and on mammalian models of dystrophinopathies, more specifically upon the mouse that is the most commonly used animal model in pre-clinical studies, and we placed a particular focus on the physiology and anatomy of the retina, in addition to biochemistry and subcellular processes.

## 2. *DMD* gene, dystrophins and associated proteins

The diagnosis of dystrophinopathy is usually based on a combination of clinical and laboratory tests with a genetic confirmation when available (Birnkranz et al., 2018). DMD is suspected if an abnormal muscle function is observed in a male child. Serum levels of creatine kinase are elevated in DMD patients and constitute a relevant biomarker

of the disease. Moreover, histological examination of muscle tissue and electromyography may be used to exclude other causes of muscle weakness (Bushby et al., 2010). The molecular diagnosis includes the polymerase chain reaction (PCR) test that is largely used to detect exonic deletions in the *DMD* gene (Beggs et al., 1990; Chamberlain et al., 1988; den Dunnen and Beggs, 2006). In addition, multiplex ligation probe amplification (MLPA) and DNA sequencing are used to identify small exonic and intronic genetic alterations (Duan et al., 2021).

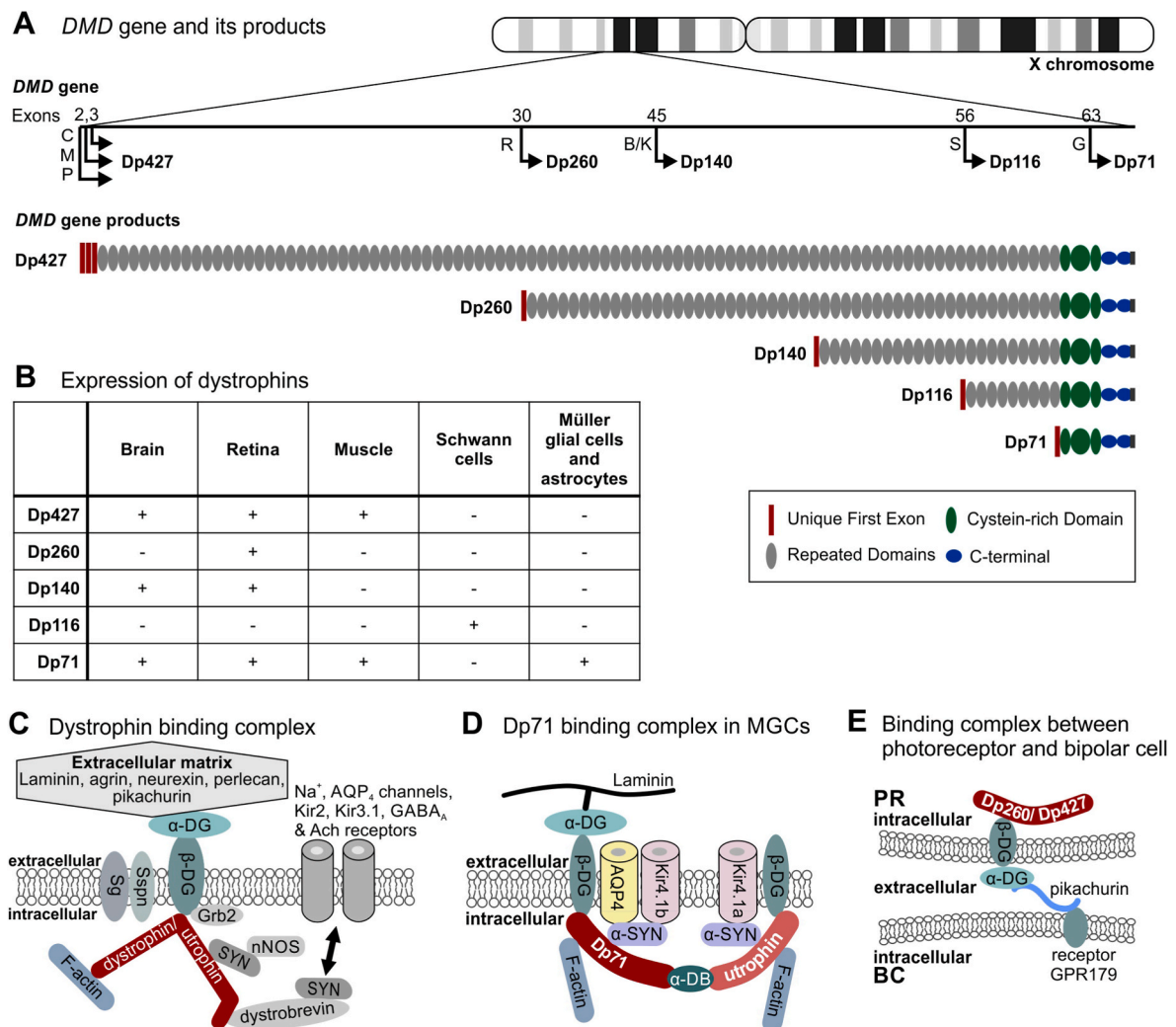
### 2.1. One gene, several dystrophin proteins

The X-linked (Xp21) *DMD* gene is the largest of approximately 30,000 genes of the human genome (Hood and Rowen, 2013; Koenig et al., 1987). It spans 2.4 Mb producing a full 14-kb transcript (Koenig et al., 1988), as well as shorter transcripts produced by internal promoters and/or alternative splicing, responsible for the presence of shorter C-terminal dystrophins. Fig. 1 A shows the X-linked *DMD* gene containing 79 exons with an extensive coding region (Ahn and Kunkel, 1993; Bettecken et al., 1992) including seven internal promoters. The three first internal promoters (C, M and P) are responsible for the differential expression of full-length dystrophins of 427 kDa (Dp427) first characterized in cerebral tissue (Dp427c), skeletal muscles (Dp427m) and Purkinje cells (Dp427p). Each of these full-length dystrophins has a specific first exon and comprises about 3600 amino acids distributed over 180 nm in length. These full-length dystrophins contain four functional domains: i) the N-terminal domain, which binds to actin; ii) a rod-shaped domain with spectrin-like structural repeats, responsible for protein flexibility and comprising additional subdomains involved in binding to actin, neuronal nitric oxide synthase, cholesterol and microtubules (Allen et al., 2016; Zhao et al., 2016); iii) a cysteine-rich domain, required for interaction with the transmembrane dystroglycan complex and calmodulin; and iv) a C-terminal domain involved in the binding to other cytosolic and signaling proteins (Michalak and Opas, 1997; Tinsley et al., 1993b, 1994). As shown in Fig. 1 A, the other four internal promoters of the *DMD* gene are responsible for the production of smaller dystrophins, also named according to their molecular weight: Dp260, Dp140, Dp116, and Dp71 (Sadoulet-Puccio and Kunkel, 1996). Their respective transcriptional start sites are in introns 29 (referred to as R: retina), 44 (B/K: brain/kidney), 55 (S: Schwann cell) and 62 (G: general). They are expressed in a tissue- and cell-dependent manner, responsible for the transcription of shorter mRNAs translated into non-muscle dystrophins with truncated N-terminus but sharing a common C-terminal domain.

Fig. 1 B shows that the R promoter (leading to expression of Dp260) is exclusively activated in the retina. The B/K promoter initiates Dp140 expression in kidney, brain and retina. The S promoter is active in Schwann cells and results in the selective expression of Dp116 in the peripheral nerves, yet its mRNA has been detected in brain and retina (García-Cruz et al., 2022). The G promoter is responsible for the expression of Dp71 in neurons and glial cells in brain (Daoud et al., 2008) and at least in glial cells in retina, and several other tissues (Ahn and Kunkel, 1993; Muntoni et al., 2003) including liver, testis, lung, kidney (Bar et al., 1990) and skeletal muscles (Kawaguchi et al., 2018).

### 2.2. Splice variants of dystrophins

Several alternative splicings of specific exons, exon junctions and inclusions of intronic sequences have been characterized in the *DMD* gene. Most of these modifications give rise to smaller isoforms, or splice variants, which lack specific portions of the dystrophin mRNA and induce dystrophin proteins with modified carboxy terminus, and their expression appears to be regulated at least during the postnatal development of the CNS (Bies et al., 1992; Feener et al., 1989; García-Cruz et al., 2022; Lidov and Kunkel, 1997). Splicing events have been particularly documented for Dp71 in brain and retina, in which three main subfamilies including a dozen of Dp71 isoforms have been



**Fig. 1. Dystrophin-gene products and their expression in central nervous system.** (A) Organization of the *DMD* gene and *DMD*-gene products. The exon numbers, indicated above the gene, point to the exons that are first transcribed from the different internal promoters and the arrows indicate where transcription starts for the corresponding dystrophin proteins. A schematic representation of the modular structure of each dystrophin is shown below. Dp140 is not aligned with its promoter because its translation starts in exon 51. The N-terminal parts of dystrophins are different, but all dystrophins share a common C-terminus. Dystrophins are named according to their respective molecular weights (427, 260, 140, 116 and 71 kDa). (B) A table summarizing the tissue and cell-specific expression of dystrophins in the nervous system and muscle. (C) Schematic representation of the general dystrophin-associated proteins (DAPs) that form scaffolding complexes in a variety of tissues. The diagram highlights the main molecular connection with the transmembrane dystroglycan complex (composed of the extracellular  $\alpha$  and transmembrane  $\beta$  dystroglycans -DG-), which provides a bridge between extracellular-matrix proteins and intracellular proteins, as well as dystrophins' binding to other cytosolic proteins such as syntrophins and dystrobrevins. Depending on the tissue and/or cell type where these complexes are expressed, they may contribute to the clustering and/or stabilization of a variety of ion channels and membrane receptors. As indicated, the utrophin paralogue may also be a component of such complexes, as shown at the neuromuscular junction where it interacts with acetylcholine receptors. (D) Diagram showing the specific Dp71-associated complex in retinal Müller Glial Cells, including critical interactions with the AQP4 water channels and Kir4.1 potassium channels. The utrophin-associated complex is also shown. (E) Diagram showing the organization of the dystrophin-associated complex in photoreceptor (PR) to bipolar cell (BC), including critical interactions with the pikachurin binding receptor GPR179. C and D are adapted from [Perronnet and Vaillend \(2010\)](#) and [Tadayoni et al. \(2012\)](#), respectively. E is based on [Omori et al. \(2012\)](#) and [Orlandi et al. \(2018\)](#).

reported ([Aragón et al., 2018](#); [Austin et al., 1995](#)). Skipping of exon 78 is a main splicing-out event affecting Dp71, giving rise to the Dp71f family of isoforms, while isoforms with preserved exon 78 are members of the Dp71d family. Importantly, it was shown that the Dp71f family predominates in the retina, while Dp71d isoforms predominate in the brain ([Aragón et al., 2018](#)). Another N-terminal isoform of Dp71, Dp40 (also called apo-dystrophin-3), is lacking the dystrophin C-terminus; it has been localized in brain synapses ([Fujimoto et al., 2014](#); [Romo-Yáñez et al., 2020](#); [Tinsley et al., 1993a](#); [Tozawa et al., 2012](#)) and we have detected its mRNA in retinal photoreceptors ([García-Cruz et al., 2022](#)). Interestingly, Dp40 mRNA was the main dystrophin transcript in mature cone photoreceptors, but presence of the Dp40 protein in these cells is still unknown.

We also have recently uncovered the presence of a new exon within intron 51 (E51b), which may be included in the mRNAs of Dp427, Dp260 and Dp140 in the mouse retina, at least in photoreceptors, yet a putative expression at the protein level has not been demonstrated. Importantly, we also have evidenced inclusions of intronic sequences with stop codons leading to the presence of transcripts with elongated exons 40 and/or 41 (E40e, E41e) in both retina and brain, which are translated into truncated Dp427 and Dp260 proteins lacking their C-terminus (N-Dp427 and N-Dp260) ([García-Cruz et al., 2022](#)). Interestingly, expression levels of these new dystrophins are regulated during postnatal retinal development. However, their specific localization and function remain to be specified, as they lack the domains required to interact with key dystrophin-associated proteins.



### 2.3. Dystrophin-associated complexes

The dystrophin protein is a core component of an actin-based membrane-bound glycoprotein complex connecting intra- and extracellular components (Ahn and Kunkel, 1993; Brown, 1997; Gao and McNally, 2015; Hoffman et al., 1987). The dystrophin-associated glycoprotein complex (DGC; Fig. 1 C) includes the transmembrane dystroglycan complex ( $\alpha$ - and  $\beta$ -DG), sarcoglycans, sarcospan, syntrophins (SYN) and dystrobrevins located in the intracellular portion of the complex (Haenggi and Fritschy, 2006; Montanaro and Carbonetto, 2003). Importantly, distinct DGCs composed of various isoforms of dystrophin-associated proteins (DAPs) have been described in different tissues and cells, which may interact with different membrane ion channels or receptors subserving distinct cellular functions (Blake et al., 2002; García-Cruz et al., 2022; Perronnet and Vaillend, 2010).

In skeletal muscle, the Dp427-associated DGC connects the cytoskeleton to the extracellular matrix (O'Brien and Kunkel, 2001), interacts with sodium channels, and contributes to cell membrane integrity during cycles of muscle fiber contraction and elongation (Blake and Kröger, 2000; Chelly et al., 1990a; Koenig et al., 1988). DMD patients, who all lack Dp427, therefore show severe and progressive muscular dysfunction (Hoffman et al., 1987). In contrast, brain Dp427c is expressed in central inhibitory synapses, where the DGC interacts with GABA<sub>A</sub> receptors to stabilize their clustering, thus contributing to their functional role in neuronal inhibition and cognitive functions (Fritschy et al., 2012; Perronnet and Vaillend, 2010).

The shorter dystrophins can also interact with DGC components in distinct cell types. The Dp71-associated complex has been well characterized in glial cells, and it appears to be similar in brain perivascular astrocytes and retinal Müller glial cells (MGCs) (Belmaati Cherkaoui et al., 2021; Benabdesselam et al., 2012; Claudepierre et al., 2000; Connors and Kofuji, 2002; Fort et al., 2008; Giocanti-Auregan et al., 2016; Haenggi and Fritschy, 2006; Nicchia et al., 2008; Tadayoni et al., 2012). Fig. 1 D shows a schematic representation of the protein complex in the MGCs, where Dp71 is a central component. In these cells, Dp71 and  $\alpha$ -syntrophin are involved in the clustering of aquaporin-4 (AQP4) and Kir4.1 potassium channels. The enrichment of these channels in MGC endfeet, contacting vascular elements and part of the limiting membranes, suggests that they contribute to the function of the blood-retina barrier. AQP4, a selective water transport protein, is functionally coupled with Kir4.1, thus contributing to both water and potassium homeostasis. Defective AQP4 channels are also a common feature in muscle tissue of DMD patients (Frigeri et al., 2002). In addition to structural functions, dystrophins and associated complexes may therefore control critical physiological cell functions in muscle and in the central nervous system. The photoreceptor DGC (Fig. 1 E) has Dp260 and/or Dp427 as the central component connecting the transmembrane dystroglycan complex ( $\alpha$ - and  $\beta$ -DG), which binds the extracellular matrix-like retinal protein pikachurin, thus linking the dystroglycan complex to the membrane receptor GPR179 at bipolar cell dendrites (Omori et al., 2012; Orlandi et al., 2018). The photoreceptor DGC may therefore be considered a part of the bridge that connects photoreceptors to bipolar cells.

Recent transcriptomic-based characterization of dystrophins and DAPs in immature and mature retina revealed that several dystrophins and DAPs mRNAs may be co-expressed in a given cell type, perhaps reflecting an involvement in distinct subcellular domains. They may also be differentially expressed in rod and cone photoreceptors, and developmentally regulated during postnatal photoreceptor maturation (García-Cruz et al., 2022). Although this raises interesting new working models to address the orchestrated involvement of multiple dystrophins during retina formation, a validation of these observations at the protein level is still missing.

### 3. The natural history and genetic basis of dystrophinopathies

Altered Dp427 expression and/or function at the inner membrane of muscle fibers, with or without the additional deficiency of other dystrophins, causes DMD, BMD, or DMD-associated dilated cardiomyopathy (Bonilla et al., 1988; Darras et al., 1993). Out-of-frame genetic mutations in the DMD gene create a stop in the mRNA, which prevents the production of one to several dystrophins depending on the position of the genetic alteration, and are responsible for the severe DMD phenotype (Aartsma-Rus et al., 2006). In-frame genetic mutations in the DMD gene can result in partially functional dystrophins with preserved functional domains and usually result in the milder BMD phenotype. The prevalence of DMD is nearly three times higher than the prevalence of BMD (Romitti et al., 2015), due to the higher frequency of out-of-frame genetic mutations (Flanigan et al., 2009). In DMD-associated dilated cardiomyopathy, the genetic alteration preferentially affects the function of the dystrophin in cardiac muscle cells, leading to heart failure over time while enough Dp427 is produced in skeletal muscles preventing major muscular dysfunction (Berko and Swift, 1987; Cohen and Muntoni, 2004; Ferlini et al., 1999; Towbin et al., 1993).

#### 3.1. The natural history of dystrophinopathies

The DMD patient is typically born without detectable muscle impairments, but mobility symptoms appear in early childhood (Pane et al., 2013). Unfortunately, in families with no history of dystrophinopathies the definitive diagnosis is usually established at age between 4 and 5 years (Ciafaloni et al., 2009). The late diagnosis can delay the start of treatment and genetic counselling, increasing the risk that affected boys are born in subsequent pregnancies (Appleton and Nicolaides, 1995; Gardner-Medwin et al., 1978). Mobility is progressively lost because of increasing muscular weakness with loss of ambulation at age between 8 and 13 years. The patients often die during the second or third decade of life due to cardiorespiratory failure (Emery, 1998). The position of the genetic mutation may influence disease's progression (Brogna et al., 2019; Chesshyre et al., 2022; Coratti et al., 2019; Desguerre et al., 2009).

The main clinical outcome described in DMD/BMD is a muscular degeneration, since Dp427 has a crucial function in maintaining the integrity of the cell membranes during the contraction and stretching cycles of muscle fibers (Blake and Kröger, 2000; Ohlendieck et al., 1991). However, dystrophins are also strongly expressed in other organs, including the central nervous system (Chelly et al., 1990b).

DMD is associated with a variety of cognitive dysfunctions and neuropsychiatric outcomes (Fitzpatrick et al., 1986; Mehler, 2000), including intellectual disability, autism-spectrum disorders, attention deficit hyperactivity disorder and obsessive-compulsive disorder (Colombo et al., 2017; Fujino et al., 2018; Hendriksen and Vles, 2008; Wu et al., 2005). These deficits may have profound effects on many aspects of the neurological development, therefore affecting the patients' education. Importantly, the neurodevelopmental delay associated with cognitive abnormalities may be detected at very early stages of the disease (Pane et al., 2013), even before muscular impairments are observed. Children with neurodevelopmental delay of unknown genetic origin may thus be redirected for additional diagnostic tests such as a genetic evaluation to determine presence of DMD.

Dystrophins are also expressed in retinal neurons (D'Souza et al., 1995), glial cells and astrocytes (Claudepierre et al., 1999, 2000), and they are required for normal processing at several levels of the visual system (Schmitz and Drenckhahn, 1997). DMD is associated with abnormal standard electroretinography (ERG), with, however, no major visual deficit (Pillars et al., 1993; Sigesmund et al., 1994).

#### 3.2. Genetic bases of dystrophinopathies

Dystrophinopathies are inherited in an X-linked recessive manner.

Most of the male patients receive the defective gene from their mother, but one third of cases are caused by *de novo* mutations (Zatz et al., 1977). Heterozygous female carriers can show disease manifestations that may involve the muscle, the central nervous system, and/or the cardiac function (Bushby et al., 1993; Fitzgerald et al., 1999; Ishizaki et al., 2018; Lim et al., 2020; Mercier et al., 2013; Papa et al., 2016). However, because this is an allelic X-linked recessive genetic disease, estimates of frequency generally do not include affected females or female carriers. In very rare cases, affected females are homozygous (Fujii et al., 2009).

Genetic deletions (Bartlett et al., 1988; Wapenaar et al., 1988) and duplications of one or several exons in sequence (Hu et al., 1988, 1990) occur in most patients (>60% and >5% of cases, respectively). The middle part of the *DMD* gene, around exons 45 to 55, is more frequently affected (Bladen et al., 2015; Flanigan et al., 2009; Juan-Mateu et al., 2015; Oshima et al., 2009) and the majority of DMD patients therefore display genetic mutations downstream of exon 30, thus affecting at least Dp427 and the retina-specific Dp260. Duplications are less common and more likely occur upstream of exon 30, with a high frequency of a single duplication of exon 2 (Bladen et al., 2015; White et al., 2006), which only affects the full-length (Dp427) dystrophins. Small deletions, insertions or point mutations account for approximately 20% of cases (Duan et al., 2021); 50% of all small mutations are nonsense mutations (Bladen et al., 2015) that cause a transition into a stop codon. Importantly, the type of genetic mutation (Magri et al., 2011) as well as the size of the deletion/duplication (Davies et al., 1988) are not associated with the severity of the clinical phenotypes, which rather appear to be influenced by the position of the genetic mutation (Magri et al., 2011).

The position of proximal and distal mutations also influences the severity of cognitive deficits (Magri et al., 2011). Approximately 30% of the patients with DMD have intellectual disability characterized by an IQ below 70 (Billard et al., 1998; Bresolin et al., 1994), with increasing severity when mutations are distal and with the most severe phenotypes when the smallest dystrophin (Dp71) is affected in addition to the others (Daoud et al., 2009; Moizard et al., 1998). Genotype-phenotype relationships are still unclear regarding other neuropsychiatric disturbances, but their presence and severity seem to depend on mutation position (Maresh et al., 2022; Ricotti et al., 2016b). Previous studies showed that a selective disruption of Dp427 expression in humans may affect specific types of memory and executive functions, as well as verbal skills and social and emotional behaviors (Cyrulnik and Hinton, 2008; Hinton et al., 2000, 2006; Ricotti et al., 2016b; Wicksell et al., 2004). This is also supported by preclinical studies in the Dp427-deficient *mdx* mouse model of DMD that displays memory deficits as well as emotional and social disturbances, which have been associated with altered synaptic plasticity in various brain structures (Miranda et al., 2015; Sekiguchi et al., 2009; Vaillend et al., 1995, 2004; Vaillend and Chausseuot, 2017). Studies of mouse models and cell lines with selective or additional loss of Dp140 and Dp71 also support the hypothesis that distal mutations may affect distinct brain functions, including glial functions, and contribute to variations in phenotype severity (Chausseuot et al., 2019; Daoud et al., 2008; Lange et al., 2022; Saoudi et al., 2021).

The retinal disturbances also vary depending on the position of the genetic mutation, with more profound alterations being associated with distal mutations and thus with the occurrence of more severe neurodevelopmental disturbances (Ricotti et al., 2016a), suggesting that ERG is a potential biomarker, or signature, of protein-specific central deficits in DMD. The current knowledge and working hypotheses regarding the roles of the distinct dystrophins in retinal physiology and visual functions is detailed in the next sections.

## 4. Dystrophin-deficient animal models

### 4.1. Non-mammalian models

Animal models of dystrophinopathies include non-mammals, such as the dystrophic fruit fly (*Drosophila melanogaster*; see Kreipke et al., 2017

for review) or zebrafish with a nonsense mutation at the N-terminal domain of the dystrophin (Berger and Currie, 2012), which have helped to understand some of the molecular interactions and biochemical functions of dystrophins (de León et al., 2005; Neuman et al., 2001; Plantié et al., 2015). They have also allowed testing small molecules to modulate phenotypes and exon-skipping strategies to rescue dystrophins expression (Berger et al., 2011; Kawahara and Kunkel, 2013; Kunkel et al., 2006; Pantoja and Ruohola-Baker, 2013; Zayniddinova et al., 2021). The greatest advantage of these models relies on their early and rapid development, rapidly providing a large number of animals with genetic modifications. Zebrafishes have been largely used to investigate retinal abnormalities caused by different types of inherited retinal diseases (Fadool and Dowling, 2008; Perkins, 2022) and can be also relevant for DMD (Van Epps et al., 2001), considering that some molecular components of the photoreceptor to bipolar cell binding dystrophin complex have been shown to be conserved in vertebrates (Sato et al., 2008). Although the possibility of studying the expression pattern of specific retinal dystrophins in zebrafish retina has been earlier reported (Bolaños-Jiménez et al., 2001), the investigation of functional phenotypes caused by DMD in the visual system of this animal model has not been reported yet.

The fly *Drosophila melanogaster* is also considered a relevant model for studying the role of muscle dystrophins and CNS dystrophins (Bogdanik et al., 2008; Dekkers et al., 2004; Fradkin et al., 2008; Pilgram et al., 2010; van der Plas et al., 2006). Recently, degenerative processes have been reported in the retina of *Drosophila melanogaster* lacking functional large dystrophin (Dp427-like) protein (Catalani et al., 2021). The visual phenotype also revealed alterations in visual behavior in the mature visual system of a mutant fly associated with decreased responsiveness to light without mobility defects.

### 4.2. Mammalian models

Several mammalian models have also been developed (see McGreevy et al., 2015 for review), including recent developments in pig (Stirm et al., 2022), rat (Caudal et al., 2020), dog (Zayniddinova et al., 2021) and humanized mouse models (Aartsma-Rus and van Putten, 2019). Dystrophin-deficient mice have been widely used for decades to study muscular dystrophy as well as their associated comorbidities including brain and retinal defects. Interestingly, the generation of a variety of genetically modified mouse models with mutations in different parts of the *Dmd* gene have contributed to a better understanding of the complex genotype-phenotype relationships associated with DMD (Rodrigues et al., 2016). In this review, we therefore only discuss these mouse models.

The first described dystrophin-deficient mutant mouse was the *C57BL/10ScSn-Dmd<sup>mdx</sup>/J* (*mdx*) or X-chromosome-linked muscular dystrophy model (Bulfield et al., 1984). This mouse displays a spontaneous nonsense mutation in exon 23 causing premature termination of the full-length dystrophin mRNA, resulting in the selective loss of Dp427 (Sicinski et al., 1989). It is worth mentioning that the expression of brain Dp71 has also been reported to be reduced in these mice, which was associated with an altered blood-brain barrier (Nico et al., 2004). This model has been extensively used to study the roles of muscle and brain Dp427 and for preclinical assessment of therapies. Since then, several other mouse lines with a *C57BL/6* background and with mutations in distinct locations in the *Dmd* gene have been generated by chemical (N-ethylnitrosourea) mutagenesis followed by genetic crosses. This allowed the development of new mutant lines that were designated *mdx<sup>5Cv</sup>*, *mdx<sup>2Cv</sup>*, *mdx<sup>4Cv</sup>* and *mdx<sup>3Cv</sup>*, and that carry specific alleles corresponding to proximal to distal mutations distributed along the *Dmd* gene (Chapman et al., 1989; Cox et al., 1993; Im et al., 1996). These mouse lines have dystrophic phenotypes but compared to the original *mdx* mouse (with selective Dp427 loss), all but the *mdx<sup>5Cv</sup>* mutations are associated with additional, cumulative, loss of different dystrophins, thus providing interesting animal models to address the role of

non-muscle dystrophins and the complex genotype-phenotype relationships underlying DMD neurobiology.

Table 1 shows the mouse models of DMD and a list of the respective dystrophins that are absent (–), spared (+) and drastically reduced but with a low-level residual expression (↓). It includes other transgenic mouse models such as the exon 52-deleted *mdx52* mouse (Araki et al., 1997), which shows a profile of dystrophins expression similar to that of *mdx*<sup>4Cv</sup> mice, i.e. a lack of Dp427, Dp260 and Dp140, but preserved expression of Dp116 and Dp71. *Mdx*<sup>4Cv</sup> and *mdx52* models have a critical translational value as their mutation position corresponds to a hotspot region of the *DMD* gene affected in about 60% of the human DMD population and associated with cognitive deficits and retinal anomalies (Ricotti et al., 2016a). Two models displaying a full deficiency in all dystrophins, the *mdxβGeo* (Wertz and Füchtbauer, 1998) and the *Dmd*-null mice (Kudoh et al., 2005), may provide new insights in processes and mechanism that are altered in the central nervous system due to the absence of all dystrophins, comparable to those found in a relatively small (<10%), but severely affected subpopulation of DMD patients. These models are different from the *mdx*<sup>3Cv</sup> mice in terms of dystrophin expression. The *mdx*<sup>3Cv</sup> is also expected to lack expression of all dystrophins but may display low-level residual expression of functional dystrophins (Daloz et al., 2001; Li et al., 2008, 2010).

Finally, The Dp71-null mouse is the only model with a selective loss of one C-terminal dystrophin, Dp71, due to replacement of the Dp71 first and unique exon and a part of the concomitant intron with a beta-galactosidase reporter gene (Sarig et al., 1999). It has been used to better understand the role of this small dystrophin in brain and retinal glial-vascular mechanisms (Barboni et al., 2020b; Belmaati Cherkaoui et al., 2021; Benabdesselam et al., 2012, 2019; Claudepierre et al., 2000; Daloz et al., 2003; Fort et al., 2008; Nicchia et al., 2008; Sene et al., 2009; Vacca et al., 2014, 2016) and to evaluate the impact of Dp71 loss on brain plasticity and cognitive functions (Chausseu et al., 2019; Helleringer et al., 2018).

In summary, dystrophin-deficient mouse models offer a unique possibility to study the variety of phenotypes associated with DMD. During the last three decades, the dystrophin-deficient mouse models have provided key information regarding the molecular and cellular bases of the retinal alterations and visual defects in DMD, which will be further detailed in the next sections.

## 5. Cellular functions of dystrophins in the retina

The visual processing in vertebrates starts with retinal photoreceptors: both cones and rods hyperpolarize in the presence of light after phototransduction. Although they show anatomical and functional differences, both cones and rods carry out the first stages of visual information processing, sending visual signals to On- and Off-bipolar cells and to horizontal cells (Boycott and Wässle, 1991; Burger et al., 2021; Dowling and Boycott, 1966; Kolb, 1970; Kolb et al., 1995). This initial retinal network is a site of expression of dystrophins Dp427, Dp260 and Dp140 (Claudepierre et al., 1999; Daloz et al., 2001; Rodius et al., 1997; Ueda et al., 2000). These dystrophins appear to be mainly expressed at the photoreceptor ribbon synapses (Blank et al., 1999; Kameya et al., 1997; Ueda et al., 1995; Wersinger et al., 2011) where cones and rods contact On-bipolar cells and horizontal cells (Regus-Leidig and

Brandstätter, 2012; Sterling and Matthews, 2005), but have also been detected at the flat synapse where cones contact Off-bipolar cells (Kolb, 1970). In addition, dystrophin Dp71 is required for proper retinal glial cells' functions (Claudepierre et al., 2000; Daloz et al., 2003). Fig. 2 A summarizes the main accepted expression pattern of dystrophins in the retina and Fig. 2 B displays the specific distribution of dystrophins at the ribbon and flat synapse of the photoreceptors.

### 5.1. Retina-specific Dp260

Dp260 is only detected in the retina where it is abundantly expressed (D'Souza et al., 1995). Dp260 is structurally similar to the full-length Dp427 (see Fig. 1 A), except that it lacks the first N-terminal actin-binding domain. Dp260 is similarly expressed in the outer plexiform layer (OPL) in mouse (D'Souza et al., 1995; Wersinger et al., 2011) and human retina (Drenckhahn et al., 1996; Pillers et al., 1993). Dp260 expression is markedly and progressively increased in the developing retina, consistent with the progressive establishment of synaptic functions (Rodius et al., 1997), strongly suggesting that Dp260 is important in synaptogenesis and synaptic integrity. Its expression decreases when photoreceptors are no longer functional (Claudepierre et al., 1999). Importantly, our group (Barboni et al., 2021a, 2021b) and other groups (D'Souza et al., 1995; Pillers et al., 1993; Ricotti et al., 2016a; Ulgenalp et al., 2002) have demonstrated that the absence of Dp260 is associated with a negative electroretinogram in DMD patients, and reduced b-wave amplitude in DMD mouse models, suggesting a disturbed communication between photoreceptors and second order retinal neurons at the first synapse of visual processing.

Dp260 is found around the invaginating (ribbon) synapse (Blank et al., 1999; Kameya et al., 1997; Ueda et al., 1995; Wersinger et al., 2011), a specialized glutamatergic synaptic structure formed by the photoreceptor terminals and the dendritic tips of depolarizing (On-) bipolar cell and horizontal cells, in both rods (Fig. 2 B upper panel) and cones (Fig. 2 B lower panel) (Sterling and Matthews, 2005). The rod synapses are almost exclusively invaginating synapses, connecting rod terminals to depolarizing rod bipolar cells that express metabotropic glutamate receptors (mGluR6). Cones establish invaginating synapses with On-cone bipolar cells, and basal (flat) connections with hyperpolarizing bipolar cells (Off-cone bipolar cells), except those of the b2 subtype which are also invaginated (DeVries et al., 2006). Off-bipolar cells express ionotropic glutamate (AMPA and kainate) receptors (Mariani, 1984; Morigiwa and Vardi, 1999; Vardi et al., 1998), which are sign-conserving: as photoreceptors, Off-bipolar cells are hyperpolarized by light increments. Activation of mGluR6 receptors leads to a sign-inversion and thus to a depolarization of the post-synaptic On-bipolar cells by light increments (Morigiwa and Vardi, 1999; Nakajima et al., 1993).

As depicted in Fig. 1 E, several lines of evidence suggest that Dp260 is likely the main dystrophin linking transmembrane dystroglycan to extracellular pikachurin and bipolar-cell GPR179 orphan receptors (Orlandi et al., 2018) at the ribbon synapse, at least in mature rod photoreceptors (García-Cruz et al., 2022). This is also supported by the observation that Pikachurin-deficient mice show similar functional (ERG) changes as mice lacking both Dp427 and Dp260, but not as mice lacking Dp427 only (see section 7 for more detailed descriptions of ERG

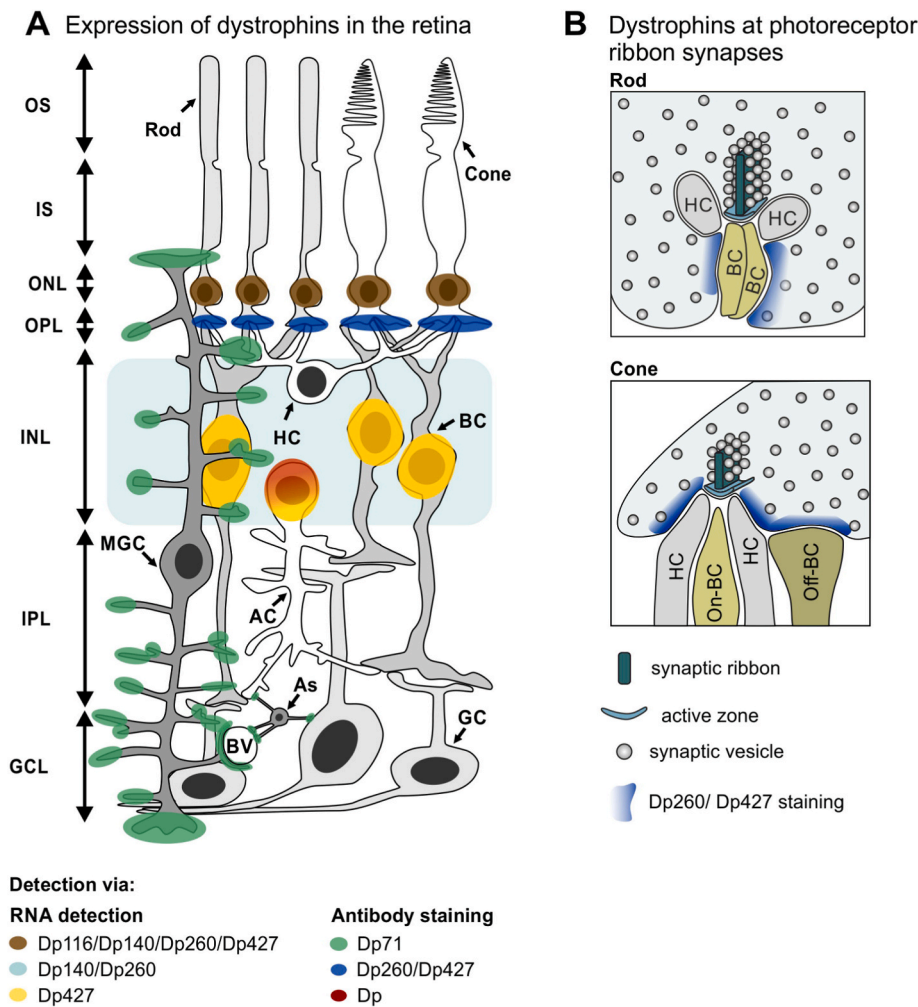
Table 1

Expression pattern of retinal dystrophins in WT (C57BL/6) and dystrophin-deficient mouse lines.

	C57BL/6	<i>mdx</i>	<i>mdx</i> <sup>5Cv</sup>	<i>mdx</i> <sup>2Cv</sup>	<i>mdx52</i>	<i>mdx</i> <sup>4Cv</sup>	<i>mdx</i> <sup>3Cv</sup>	<i>mdx-β-geo</i>	<i>Dmd</i> -null	Dp71-null
Mutation position	\	Exon 23	Exon 10	Intron 42	Exon 52	Exon 53	Intron 65	Exon 63	<i>Dmd</i> -gene deletion	Dp71 first unique exon
Dp427	+	–	–	–	–	–	↓	–	–	+
Dp260	+	+	+	–	–	–	↓	–	–	+
Dp140	+	+	+	+	–	–	↓	–	–	+
Dp71	+	+	+	+	+	+	↓	–	–	–

+: normal expression; -: no expression; ↓: low-level residual expression.





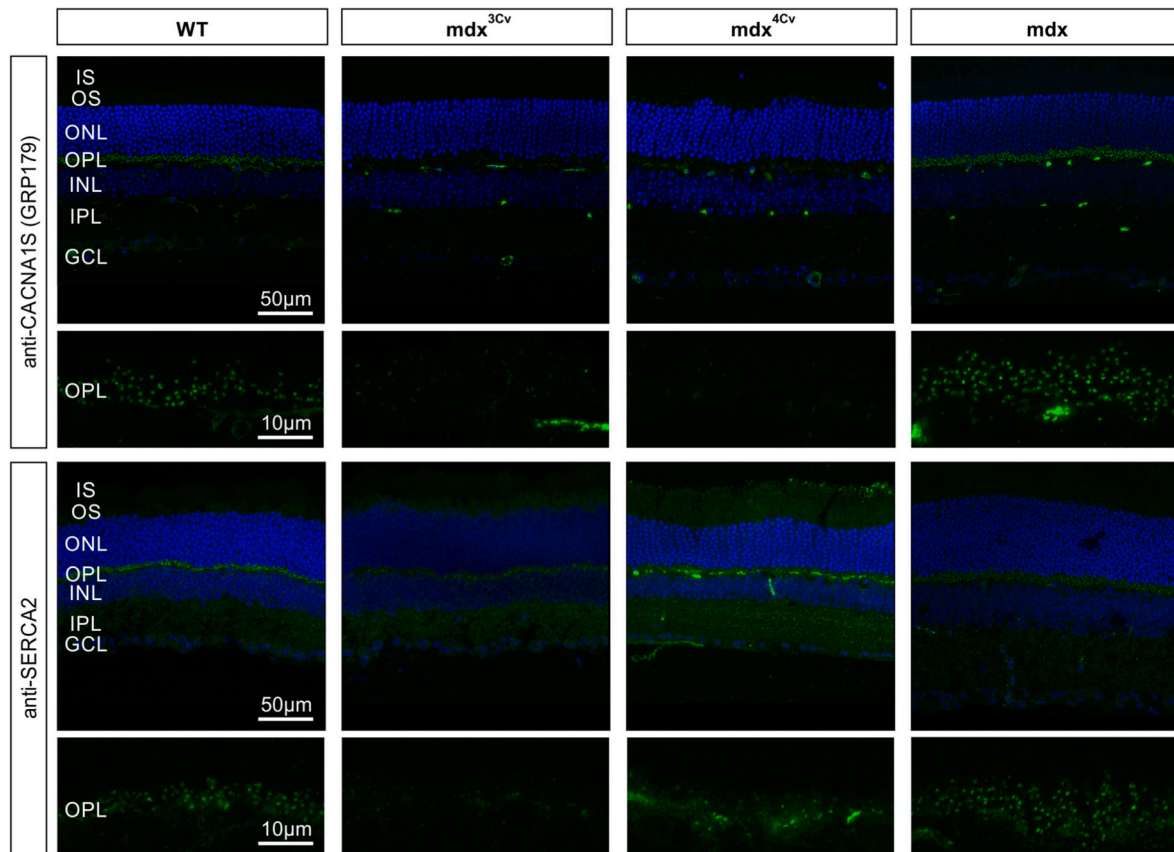
**Fig. 2. Retinal expression of dystrophin proteins in mature retina.** (A) Dystrophins are expressed in the outer plexiform layer (OPL) and in the inner nuclear layer (INL). Dp427 and Dp260 have been detected at the photoreceptor synapses and in the soma of bipolar and/or amacrine cells. It is not known which cells express dystrophins in the INL (blue shaded background). Müller glial cells (MGC) express Dp71. (B) Localization of Dp427 and Dp260 at the photoreceptor synapse. Expression of dystrophin proteins at the rod terminal (above), rod to rod-bipolar cell ribbon synapses, and at the cone terminal (below). AC = amacrine cell; BC = bipolar cell; GC = ganglion cell; HC = horizontal cell; MGC = Müller glial cell; BV = blood vessels; As = astrocytes. The upper panel in B has been adapted from Barboni et al. (2021b).

phenotypes). The absence of pikachurin induces alterations of the ultrastructure of the photoreceptor to On-bipolar cell synapse and affects both the dark-adapted (rod-dominated) and light-adapted (cone-driven) ERG responses (Nagaya et al., 2015; Sato et al., 2008). Disrupting this bridge between dystroglycan and pikachurin has different consequences for the ERG depending on which component of the synaptic complex is altered. The most severe ERG phenotypes were found in *Gpr179*<sup>-/-</sup> mice (Klooster et al., 2013; Peachey et al., 2012) and photoreceptor-conditional Dystroglycan-KO mice (Omori et al., 2012; Orlandi et al., 2018), while the absence of pikachurin (Orlandi et al., 2018; Sato et al., 2008) or of Dp260, Dp427 and/or Dp140 have a more limited impact on ERG (Barboni et al., 2021b; Kameya et al., 1997; Pillers et al., 1999), even if the absence of dystrophins is associated with a large reduction of both dystroglycan and pikachurin expression (Orlandi et al., 2018). Although the dystrophin-associated complex has an important contribution in the anchoring or stabilization of Gpr179, these observations suggest that it is not the sole actor in this process (Cao et al., 2022).

Beyond these molecular working hypotheses, it is nevertheless still unknown which specific physiological mechanisms are affected by the loss of Dp427/Dp260 in photoreceptors, and whether these two dystrophins play distinct roles in these cells. A report by Specht et al. (2009) indicated that two proteins involved in calcium-induced calcium release (CICR), CACNA1S and SERCA2, are expressed at the tip of On-bipolar cell dendrites. As these proteins are also expressed in the skeletal and cardiac muscles where dystrophin plays a critical role, a possible role of retinal dystrophins in organizing a CICR complex in On-bipolar cell

dendrites can be considered. Besides its main expression in photoreceptors, a low expression of Dp427 and possibly Dp260 in bipolar cells was previously suggested (Wersinger et al., 2011), and indirect alterations of bipolar cell functions possibly also occur in the absence of Dp427/Dp260 due to the disruption of the dystrophins/dystroglycans/pikachurin/GPR179 bridge. Preliminary results (Roux et al., 2012) suggest that a lack of Dp427/Dp260 potentially indeed alters the organization of such a complex, because a strong reduction in CACNA1S and SERCA2 labeling was observed in the OPL of both *mdx*<sup>4Cv</sup> and *mdx*<sup>3Cv</sup> lacking several dystrophins, while CACNA1S and SERCA2 were normally distributed in *mdx* mice that only lack Dp427 (Fig. 3). Since then, it has been demonstrated that the CACNA1S antibody used in retinal studies (Specht et al., 2009; Tummala et al., 2014) cross-reacted with GPR179, and that bipolar cells were not expressing CACNA1S (Hasan et al., 2016). Our results with this antibody therefore indicated that the loss of Dp260 was associated with a decreased expression of GPR179. This does not preclude the existence of a CICR complex in On-bipolar cell dendritic tips, as the initial calcium entry could come from TRPM1 – many TRP channels have been involved in this kind of calcium signaling. Our preliminary data, showing a reduced expression of SERCA2 in the OPL, suggest that disruption of dystrophins, dystroglycan, pikachurin and GRP179 may affect proteins involved in calcium signaling in On-bipolar cells. Characterization of other proteins classically part of CICR complexes, such as stim1, ryanodine receptors and triadins, should be considered in future studies.





**Fig. 3.** Distribution of calcium-signaling proteins in the OPL depending in WT and *mdx* mouse lines lacking different dystrophins. Top panel: A monoclonal antibody directed against GRP179 (Abcam ab78003, now ab2862, 1/5000) provides a punctate immunoreactive signal (green) in the OPL of both WT and Dp427-deficient *mdx* retinas (see also the zoomed OPL images below), that is no longer visible in retinas from *mdx*<sup>3Cv</sup> and *mdx*<sup>4Cv</sup> mice that lack several or all dystrophins. Bottom panel: A monoclonal antibody against the sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase 2 (SERCA2) (Merck Millipore S1439, now MAB2636, 1/250) provides a similar punctate labelling in WT and *mdx* retinas, which is much weaker in retinas from *mdx*<sup>3Cv</sup> and *mdx*<sup>4Cv</sup> mice. Note that the remaining labelling in the image from *mdx*<sup>4Cv</sup> mice reflects a vascular expression. Immunofluorescence studies were performed in fresh retina following methanol post-fixation. Results have been replicated three times in each genotype. Scale bars: 50  $\mu\text{m}$  for global views, 10  $\mu\text{m}$  for OPL details.

### 5.2. Glial dystrophin: Dp71

Dp71 is expressed in Müller glial cells (MGC), astrocytes (notably around the blood vessels and the inner limiting membrane) and pericytes. Although Dp71 has a unique expression profile and does not appear to be expressed in neurons, its role in the retina is better known than those of other retinal dystrophins. Because Dp71 is generated by alternative usage of an internal promoter located at the intron between exons 62 and 63 of the *DMD* gene (Bar et al., 1990; Blake et al., 1992; Hugnot et al., 1992; Rapaport et al., 1993), its loss only affects less than 10% of the DMD patients (Oshima et al., 2009).

As described above (Fig. 1 D), Dp71 in MGCs is part of a transmembrane complex enabling the proper distribution of the inward rectifying potassium Kir4.1 channels (Connors and Kofuji, 2006; Dalloz et al., 2003; Fort et al., 2008) and of the Aquaporin-4 (AQP4) water transport proteins (Fort et al., 2008), thus regulating water homeostasis and extracellular potassium buffering in response to photochemical changes initiated by photoreceptors (Brew et al., 1986; Connors and Kofuji, 2006; Frishman et al., 1992; Frishman and Steinberg, 1989; Kofuji et al., 2000, 2002; Newman, 1987).

In the endfeet of MGCs, the dystrophin associated proteins were identified as forming a complex that contains both Dp71 and utrophin. The complex organized around Dp71 is mainly associated with lipid rafts, and its absence is correlated with a compensatory upregulation of utrophin, a redistribution of Kir4.1 and a decrease of AQP4 expression. Moreover, the selective absence of Dp71 in the retina of the Dp71-null mouse causes a morphological change of the MGC endfeet that look

looser and provokes the breakdown of the blood-retina barrier and increase in retinal vascular permeability, limiting retinal osmoregulation and mimicking a pre-edematous state (Fort et al., 2008; Sene et al., 2009; Vacca et al., 2014). These changes are associated with retinal vascular inflammation and vascular lesions, increased leukocyte adhesion and capillary degeneration. The absence of Dp71 increases expression of the vascular endothelial growth factor (VEGF) and intercellular adhesion molecule (ICAM), and the number of adherent leukocytes is also increased (El Mathari et al., 2015). Surprisingly, these phenotypes are not observed in *mdx*<sup>3Cv</sup> mice (Rendon et al., unpublished results) that display a dramatic reduction in the expression of all dystrophins including the Dp71 (Cox et al., 1993). Indeed, compared to wild-type littermates, the retinas of *mdx*<sup>3Cv</sup> mice show only 4% of normal Dp71 expression. These results suggest that the 4% residual expression of Dp71 is sufficient for the maintenance of the blood-retinal barrier and to protect the retina from the inflammation found in Dp71-null mice (Rendon et al. unpublished results).

Dp71 is also expressed in retinal astrocytes, which play an important role in the development of retinal vasculature. The absence of Dp71 is accompanied by a delay in the postnatal development of the vascular system and changes in the fine neuroanatomy of astrocytes that could be an important upstream factor at the origin of the altered postnatal vascular development associated with a decrease in vessel density compared with wild-type mice (Giocanti-Auregan et al., 2016).

In summary, Dp71 plays a major role in retinal glial-dependent processes that contribute to the structural and functional integrity of the retina. This is reflected in the ERG changes observed in Dp71-null

mice (see Section 7) and this may exacerbate the ERG defects in patients holding mutations that impede expression of Dp71 (see Section 6).

### 5.3. Full-length retinal Dp427

Dp427 is expressed in mouse (Miike et al., 1989; Zhao et al., 1991) and human (Pillars et al., 1993) retina at much lower levels compared to Dp260 (García-Cruz et al., 2022). The expression of Dp427 in the inner retina is mostly supported by RNA data, with a very strong signal at the level of rod bipolar cells using *in situ* hybridization and laser-microdissection (Wersinger et al., 2011). Just like Dp260, retinal Dp427 is found in the outer plexiform layer (OPL) of the mouse retina (Fig. 2 A). However in contrast to Dp260, that is mainly expressed in rods in the adult retina, it has been proposed that Dp427 is relatively more expressed in cone than in rod terminals (Wersinger et al., 2011) and that the Dp427p (Purkinje) isoform might predominate in retina (García-Cruz et al., 2022). Importantly, Dp427 has great clinical and therapeutic relevance for the muscle and brain conditions, because it is affected in all DMD and BMD patients.

In the brain, Dp427 has been localized to postsynaptic elements, in particular at the level of GABAergic synapses (Briatore et al., 2020; Fritschy et al., 2012; Lidov et al., 1990; Perronnet and Vaillend, 2010). Indeed, Dp427 has been found to be part of one of the scaffolding systems for the GABA<sub>A</sub> receptor (Knuesel et al., 1999; Kueh et al., 2011; Lévi et al., 2002). The size and density of GABA receptor clusters are reduced in the brain of *mdx* mice. It is, however, unlikely that Dp427 has a similar role in photoreceptor terminals since GABA receptors are not expressed in rods and their presence in mammalian cones is still a matter of debate (Deniz et al., 2019; Grove et al., 2019; Kemmler et al., 2014; Verweij et al., 2003). It should be mentioned that GABA receptors are expressed in cells that interact with the photoreceptors (Popova, 2014). For instance, subpopulations of horizontal cells make GABAergic synapses with bipolar cells in the OPL (Wu and Maple, 1998). Therefore, GABA receptors expressed in On-bipolar and Off-bipolar cells (Yang, 2004) could influence photoreceptor function. Although Dp427 mRNA was detected in bipolar cells, no specific dystrophin clusters were reported in the neurites of these retinal neurons.

Recent studies suggest that the absence of Dp427 may affect several cellular processes required for the structural and functional integrity of the retina in an age-dependent manner. In a detailed analysis of retinal gene expression, layer maturation, neural cell proliferation, apoptosis, and differentiation during embryonic and postnatal stages in the *mdx* mouse, a range of cellular abnormalities were detected, that suggest a role for Dp427 in shaping specific steps of retinal differentiation (Persiconi et al., 2020). The changes included reduced expression of genes involved in development and synaptogenesis, as well as delayed maturation of the retinal ganglion cell layer (GCL), reduced density of GABAergic amacrine cells and altered maturation of the ribbon synapses during the postnatal period. While most of the developmental changes associated with Dp427 absence were normalized in the mature tissues, the number of calretinin-positive ganglion cells was reduced in the adult retinae. This is in line with another study showing that Dp427 loss in young adult *mdx* mice is associated with cell death and impaired autophagy, with consequences on physiological cell fate, synapse stabilization and neuronal survival (Catalani et al., 2021). Apoptotic neurons were localized in the OPL, ONL and GCL, and autophagy dysfunction at photoreceptor axonal terminals and bipolar, amacrine, and ganglion cells. This indicates that the absence of Dp427 alters retinal homeostatic apoptosis/autophagy balance. An altered architecture of photoreceptor synapses was also observed in *mdx* mice in this study, and further confirmed and associated with retinal dysfunction using two dystrophic fruit-fly mutants lacking dystrophin-like proteins.

Although the absence of Dp427 was associated with retinal developmental delays, cell death and altered photoreceptor-synapse ultrastructure, the lack of an overt ERG phenotype in young adult dystrophin-deficient *mdx* mice suggests that these alterations are functionally

compensated (Pillars et al., 1999). In contrast, another study revealed a more severe ERG phenotype of old *mdx* mice (>15 months old), particularly when mice were submitted to an oxygen-induced retinopathy protocol (Bucher et al., 2019). Retinal physiological function thus appears to deteriorate in aged *mdx* mice due to additional stressors like hypoxia, which was associated with increased retinal neovascularization. This suggests progressive alterations of retinal homeostasis leading to excessive retinal neovascular changes in response to hypoxic stress, perhaps related to altered blood-retinal barrier integrity due to the absence of Dp427 in vascular smooth muscles (Nico et al., 2003). This may likely be relevant to the clinical condition of aged DMD patients with cardio-respiratory insufficiency who may suffer from hypoxia-induced vasoproliferative retinopathy (see section 6.6).

### 5.4. Dp140

The role of Dp140 as well as its localization in the nervous system is still poorly understood. Moreover, it is possible that its expression is relatively low in adult tissue compared to other dystrophins, as it has been mostly detected in the central nervous system during embryonic development (Morris et al., 1995). However, Dp140 mRNA has been detected in the soma of photoreceptors in the adult retina, but no specific antibodies are available to demonstrate protein expression at the cellular level. Our recent RNA-Seq analysis of purified photoreceptors suggests a putative low expression in adult cones (García-Cruz et al., 2022), which may be related to cone-driven ERG defects found in mouse models and in patients lacking this dystrophin (see sections 6 and 7 on ERG defects).

## 6. Alterations in the visual system of DMD patients

Since the 1990's, retinal dystrophin dysfunction or absence has consistently been associated with electroretinographic (ERG) changes. Reduced dark-adapted b-wave amplitudes in the ERGs of DMD patients have been reported repeatedly (Cibis et al., 1993; De Becker et al., 1994; Girlanda et al., 1997; Ino-ue et al., 1997; Jensen et al., 1995; Pascual et al., 1998; Pillars et al., 1999, 1993, 1995; Ricotti et al., 2016a; Sigesmund et al., 1994; Tremblay et al., 1994). Similar alterations are found in patients with inherited and acquired retinal diseases (Jiang and Mahroo, 2021), mainly in patients with congenital stationary night blindness (CSNB) (Zeitz et al., 2015) as well as in mouse models of CSNB (Pardue and Peachey, 2014; Regus-Leidig et al., 2014). In addition to the electrophysiological changes, visual perception has been found to be disturbed in DMD patients (Barboni et al., 2013, 2021a; Costa et al., 2007, 2011). In this section, we describe well-established ERG alterations caused by DMD gene mutations, and we discuss the sparser psychophysical data in DMD patients.

The ERG is an electrical mass potential originating in the retina that is initiated by the photoreceptors after stimulation by light. The ERG is generated by the activity of different groups of cells and can be easily and non-invasively recorded *in vivo* (Granit, 1933). Typically, ERGs are recorded to light flashes under dark-adapted (scotopic) conditions where the signals are mainly driven by rods or in combination with cones and under light-adapted (photopic) condition at which the responses are mainly cone-driven (Bush and Sieving, 1994; Cameron et al., 2006; Frishman, 2006; Robson and Frishman, 2014). The International Society for Clinical Electrophysiology of Vision (ISCEV) has standardized the flash and other ERG recording protocols for mutual comparability of the results among different institutions (Robson et al., 2022).

The dark-adapted full-field ERG to weak flashes of lights consist of a positive component, called b-wave, while those to strong flashes of light display an initial negative component (a-wave) representing activity of the photoreceptors and Off-bipolar cells. In that case, the a-wave is followed by the positive b-wave, that predominantly originates in On-bipolar cells (Frishman, 2006; Robson and Frishman, 2014). As mentioned above, this ERG is driven by rods and cones. Superimposed

upon the rising part of the b-wave, fast oscillations, known as oscillatory potentials (OPs), can be found, which are thought to originate at the amacrine cells through feedback interactions (Wachtmeister and Dowling, 1978). See full-field ERG components in Fig. 4 B and their respective retinal origins in Table 2.

The ERG may be used for early detection and diagnosis as well as for monitoring disease progression and the effects of therapeutic interventions. The ERG often is correlated with other clinical functional measures (e.g. visual acuity or contrast sensitivity) or with structural properties of the retina and of the visual system (e.g. quantified using optical coherence tomography). DMD typically affects ERGs (Fitzgerald et al., 1994; Pillers et al., 1993; Sigesmund et al., 1994) and visual perception is also disturbed in DMD patients (Barboni et al., 2021a; Costa et al., 2007, 2011). In addition, more severe cases of retinal alterations, such as proliferative retinopathy, have been reported in DMD patients (Bucher et al., 2019; Fagan et al., 2012; Hahn et al., 2013; Kecik et al., 2021; Lin et al., 2012; Louie et al., 2004; Ober et al., 2006; Park et al., 2019; So et al., 2012). They are likely to become more frequent as life expectancy increases in this population.

### 6.1. Dark-adapted flash ERGs

The dark-adapted ERG of DMD patients in response to weak ( $0.01 \text{ cd s/m}^2$ ) flashes can be abolished or severely reduced (Barboni et al., 2021a). The responses to standard ( $3.0 \text{ cd s/m}^2$ ) flashes show an absent or a significantly reduced b-wave when compared with the a-wave, which is usually preserved (resulting in a so-called “negative ERG”). As a result, the b:a wave-amplitude ratio is smaller than 1 (Barboni et al., 2021a; Pascual et al., 1998; Ricotti et al., 2016a) compared to normal ratios that are typically between 1 and 2 (Perlman, 1983). In addition, dark-adapted oscillatory potentials are affected in DMD patients (Barboni et al., 2021a; Cibis et al., 1993; Ricotti et al., 2016a).

Fig. 4 shows that DMD patients with genetic mutations upstream of exon 30, presumably affecting only Dp427, display less strongly affected dark-adapted ERGs compared to DMD patients with distal mutations (downstream of exon 30), which prevents expression of at least Dp260 and possibly of other C-terminal dystrophins in addition to Dp427. The

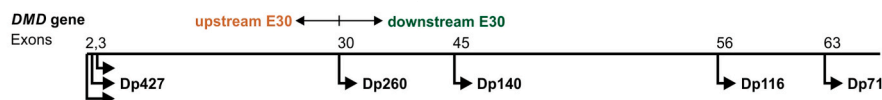
**Table 2**  
Retinal origins of ERG components.

Standard ISCEV Protocol	Component	Main retinal origin	References
ISCEV DA 0.001	b-wave	Rod On-bipolar cells	Frishman (2006)
ISCEV DA 3.00	a-wave	Photoreceptors and cone Off-bipolar cells	Robson and Frishman (2014)
	b-wave	Mainly On-bipolar cells	Frishman (2006)
	OPs	Amacrine/bipolar cells	Wachtmeister and Dowling (1978)
ISCEV LA 3.00	a-wave	Cones and Off-bipolar cells	Bush and Sieving (1994)
	b-wave	On- and Off- bipolar cells	Frishman (2006)
<b>Alternative protocols</b>			
Mesopic Rapid-On sawtooth	Positive peak	Presumably rod biased On-pathway	Barboni et al. (2013)
Mesopic Rapid-Off sawtooth	Negative peak	Presumably rod biased Off-pathway	Barboni et al. (2013)
Photopic Rapid-On sawtooth	Negative peak	Presumably cones	Alexander et al. (2003)
	Positive peak	Presumably cone-driven On-pathway	Alexander et al. (2003)
	Positive peak	Presumably cone-driven Off-pathway	Alexander et al. (2003)
Sine wave flicker (white)	First harmonic	Photoreceptor and two post-receptoral pathways	Kondo and Sieving (2001)
Red-green modulation	First harmonic	High frequencies (>30Hz): luminance pathway	Pangeni et al. (2010)
		Frequencies 4–16Hz: cone-opponent pathway	Kremers et al. (2010)

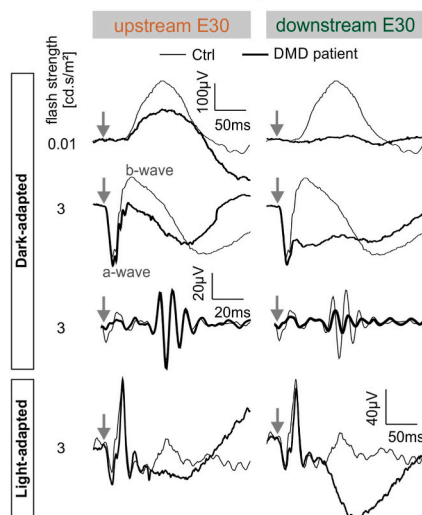
ISCEV: International Society for Clinical Electrophysiology of Vision; OPs: oscillatory potentials.

b:a ratios of the dark-adapted ERG with strong flashes is about 1.3 in patients that only lack Dp427, and about 0.6 in patients with a cumulative loss of Dp427 and Dp260 (Barboni et al., 2021a). Moreover, abnormalities of dark-adapted ERGs may be found in heterozygous female

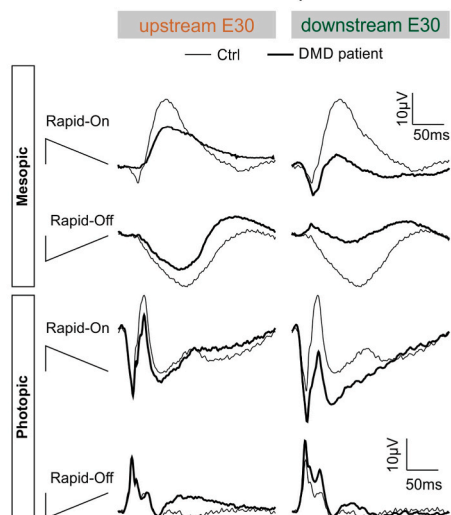
### A Position of mutations in DMD patient subgroups



### B Flash-ERGs in DMD patients



### C Sawtooth-ERGs in DMD patients



**Fig. 4. ERG abnormalities in DMD patients.** (A)

Position of the genetic mutation in the two DMD patients subgroups was either upstream of exon 30, resulting in the selective lack of Dp427, or downstream of exon 30, resulting in the lack of multiple dystrophins, at least Dp427 and Dp260 (B) Top panel: ERG responses to dark-adapted weak ( $0.01 \text{ cd s/m}^2$ ) and standard ( $3 \text{ cd s/m}^2$ ) flash stimuli according to the ISCEV standards, with 75–300 Hz bandpass filtered signals illustrated (bottom traces) representing the oscillatory potentials extracted from responses to the dark-adapted standard flash stimulus. Bottom panel: ERG responses to standard light-adapted ISCEV ( $3 \text{ cd s/m}^2$ ) flash stimuli. (C) Top panel: Rapid-On and rapid-Off ERG responses elicited by mesopic ( $1 \text{ cd/m}^2$  mean luminance) sawtooth stimuli. Bottom panel: Rapid-On and rapid-Off ERG responses elicited by photopic ( $60 \text{ cd/m}^2$  mean luminance) sawtooth stimuli. DMD patients holding mutations upstream of exon 30, DMD patients downstream of exon 30 (both shown with thick traces) and age-matched controls (thin traces) show comparable light-adapted ERG responses amplitudes while, in contrast, dark-adapted responses are reduced in DMD patients upstream of exon 30 and more severely affected in DMD patients downstream of exon 30. This is also found for mesopic rapid-On and rapid-Off responses, while only photopic rapid-On responses are altered in DMD patients. Modified from Barboni et al. (2013) and Barboni et al. (2021a).



carriers holding genetic mutations in exon 50 on one of their X-chromosomes, presumably affecting expression levels of Dp427, Dp260 and Dp140. This may be caused by random X-chromosome inactivation (Fitzgerald et al., 1999).

The described ERG alterations show that Dp260 is particularly important for normal dark-adapted ERGs. Indeed, as mentioned above, lacking Dp260 in addition to Dp427 resulted in a negative ERG, i.e. with b:a ratios smaller than 1 (Barboni et al., 2021a; Ricotti et al., 2016a; Sigesmund et al., 1994). In addition to Dp260, other DMD gene products expressed in the retina, Dp140 and Dp71, may worsen the ERG alterations in DMD patients, as suggested by Ricotti et al. (2016a). The reduced b-wave, combined with a relatively normal a-wave, indicates normal photoreceptor but altered bipolar cell function, likely associated with a disturbed signal transmission at their mutual synapse, where many dystrophins are located (see section 5). As the b-wave mainly originates in On-bipolar cells (Frishman, 2006), a reduced b:a ratio indicates a selective alteration in the synaptic transmission of the invaginating synapse where Dp427/Dp260 are located (see section 5.1). Thus, structural and functional data are in agreement with each other indicating that the On-pathway is more strongly affected than the Off-pathway. Rod bipolar cells are exclusively of the On-type; cones contact both On- and Off-bipolar cells (see Fig. 2 B).

ERG studies so far have been able to show that the lack of both Dp427 and Dp260 is linked to a negative ERG, but less is known about the effects of the smaller dystrophins on the ERG. Therefore, investigations in larger cohorts and specific subgroups with distinct genotypes are needed to confirm and detail the role of each retinal dystrophin in dark-adapted retinal physiology.

ERG measurements were less frequently performed in patients with Becker muscular dystrophy (BMD). A few studies revealed altered ERGs in BMD patients (Girlanda et al., 1997; Pillers et al., 1993, 1999; Sigesmund et al., 1994; Ulgenalp et al., 2002). These studies confirmed that the severity of the ERG alterations depends on the position of the genetic mutation in the DMD gene, with clear effects when they are downstream of exon 30, as in DMD patients. This further supports the important role of at least Dp260. However, there were exceptions: some patients with mutations upstream of exon 30 displayed abnormal ERG whereas some patients with distal mutations displayed normal ERGs (Sigesmund et al., 1994). This suggests that additional factors may influence the ERG phenotype, which has also been reported in DMD patients.

Further evidence for a key function of Dp260 in the rod pathway was recently obtained in studies where rod driven ERGs and psychophysical rod thresholds to short flashes were measured in DMD patients and normal subjects during the course of dark adaptation after a strong bleach. Generally, the psychophysical rod-driven thresholds decrease (Lamb and Pugh, 2004) and the ERG amplitudes increase (Cameron et al., 2006; Thomas and Lamb, 1999) during the course of dark adaptation. While the ERG amplitudes and psychophysical rod-driven thresholds in patients with a selective loss of Dp427 (i.e. with a mutation upstream of exon 30) were relatively comparable with those of control subjects, the rod branch of the dark adaptation curve was elevated when Dp260 was also affected (with a mutation downstream of exon 30). Furthermore, the elevated rod-driven psychophysical thresholds were significantly correlated with the b-wave amplitudes in the DMD patients (Barboni et al., 2021a). As mentioned above, ERG losses and histological alterations strongly suggest that they mainly originate at the synapse between photoreceptors and On-bipolar cells (Schmitz and Drenckhahn, 1997; Wersinger et al., 2011). This is also a likely location where dark adaptation processes occur (Cameron et al., 2006).

## 6.2. Light-adapted flash ERGs

Fig. 4 B shows examples of light-adapted flash ERGs obtained with luminance flashes. They have been consistently reported to be normal or only slightly affected in DMD patients (Barboni et al., 2021a; Cibis and

Fitzgerald, 2001; De Becker et al., 1994; Ricotti et al., 2016a; Sigesmund et al., 1994; Tremblay et al., 1994), independently of the position of the genetic mutation. Normal light-adapted ERGs were also found in heterozygous female carriers (Fitzgerald et al., 1999).

The interpretation of the physiological processes underlying the standard flash ERGs and their changes has severe limitations. A main difficulty is that flashes always result in combined stimulation of rods and cones even when the state of adaptation biases the response to be mainly driven by one of the two. Furthermore, a quantification of the stimulus strength in physiologically relevant terms (e.g. in excitation modulation of the photoreceptors) is not possible. To be able to fully control the responses of the different photoreceptor types, silent substitution stimulus techniques are available (Kremers, 2003; Kremers and Pangeni, 2012). In addition, by using combined luminance and chromatic stimulation, and with selective On- and Off-stimuli, it is possible to study post-receptoral retino-geniculate pathways in the ERGs (Kremers et al., 2014). Stimulus protocols were designed with which the responses, initiated by the cone system but involving the On-pathway (depolarizing bipolar cells) or the Off-pathway (hyperpolarizing bipolar cell) differently, were recorded. These additional possibilities were explored with DMD patients and their relatives. The results will be discussed in the next section.

## 6.3. On- and off-responses

On and Off ERG responses were recorded in DMD patients using the light-adapted long-duration flash ERG (Cibis and Fitzgerald, 2001; Fitzgerald et al., 1994, 1999). This was designed to evaluate retinal conditions with possible asymmetric abnormalities of the cone systems responding to luminance increments (On) and decrements (Off) (Alexander et al., 2003; Sustar et al., 2018) that cannot be detected using the short-duration (standard flash) stimuli (Sieving, 1993). Our group has investigated On- and Off-responses using sawtooth stimuli: rapid-on to stimulate On-pathways and rapid-off for stimulation of Off-pathways (Nagy et al., 2014). The advantage of the sawtooth stimuli over the long-duration flash stimulus is that it may be less contaminated by sudden eye movements and/or blinks that affect responses to unbearable long flashes. Furthermore, with sawtooth stimuli the state of adaptation can be better controlled. We measured responses in photopic and mesopic conditions.

Fig. 4 C shows mesopic and photopic On- and Off-responses from two DMD patient groups (with genetic alterations upstream or downstream of exon 30) and from control subjects for comparison. We observed that both On- and Off-responses were affected under mesopic conditions in patients where Dp260 is affected (i.e. with mutations downstream of exon 30). Under photopic conditions (biasing towards cone driven responses), only On-dysfunction was detected. This shows further evidence that photoreceptor-to-bipolar cell neurotransmission is affected in DMD retinas and that the retinal changes in DMD lead to the asymmetric activation of the On- and the Off-bipolar cell mechanism.

## 6.4. ERGs with heterochromatic and achromatic sine-wave flicker stimuli

Most reports in DMD patients show preserved or slightly delayed b-waves in the light-adapted flash ERG (Barboni et al., 2021a; De Becker et al., 1994; Ricotti et al., 2016a; Sigesmund et al., 1994; Tremblay et al., 1994), as shown in Fig. 4 B. However, as explained in the previous section, asymmetric cone driven (photopic) On- and Off-ERG responses have been found in DMD patients (Barboni et al., 2013; Fitzgerald et al., 1994). Moreover, cone-driven responses to heterochromatic (red-green) sine-wave flicker modulation (Barboni et al., 2016) and achromatic (white) sine-wave flicker ERGs (Barboni et al., 2020a) are also changed in DMD patients.

In healthy humans, the first harmonic components of ERGs to sine-wave luminance modulation displays a minimal amplitude at around 12 Hz, while at 30–40 Hz a maximal amplitude is observed. It has been



proposed that two independent components give rise to these ERG responses: a “sinusoidal” component is particularly large at low temporal frequency whereas a “transient” component determines the responses at high frequencies (Pangeni et al., 2010). It has been further proposed that at 12 Hz, On- and Off-luminance signals may cancel each other out (Kondo and Sieving, 2001) at least for the sinusoidal component (see Table 2). Thus, if only one of the two is selectively impaired, then larger ERG responses to 12 Hz stimuli can be expected since cancellation will not occur. This was indeed found in DMD patients because the contribution of the sinusoidal component was increased relative to that of the transient component in the ERG to sine-wave luminance modulation (Barboni et al., 2020a). Furthermore, in DMD patients responses to 12 Hz red-green heterochromatic stimulation were mainly determined by the luminance component (Barboni et al., 2016) in the stimulus, whereas in normal subjects the response was determined by the red-green chromatic stimulus component (Kremers et al., 2010). Taken together, these findings are in agreement with the notion that On-responses are affected by DMD while Off-responses are essentially spared, and that this causes changes in responses to luminance and heterochromatic sinusoidal stimuli. These retinal alterations are possibly contributing to psychophysical changes discussed in the next section.

#### 6.5. DMD-related alterations in psychophysical contrast sensitivity and in color vision

Reports on the visual consequences of the retinal defects caused by DMD are still scarce. Likewise, the knowledge about the visual consequences of specific genotypes is limited. Investigations of visual function often have relied on traditional methods, such as the Snellen visual acuity test. It was found that DMD patients with no secondary ocular diseases, such as cataract or proliferative retinopathy, showed normal visual acuity (De Becker et al., 1994; Sigesmund et al., 1994). Possibly, the use of suprathreshold contrast stimuli is less well suited to detect visual alteration caused by DMD.

Color vision in DMD patients was initially studied in a family with 20 members, including six DMD patients and four asymptomatic DMD carriers, using the Ishihara plate test (Philip et al., 1956). The results showed that 25% of the subjects were simultaneously carrying DMD and congenital (incomplete) color vision deficiencies. Other studies showed genetic linkages between DMD and deutan color blindness (absence of functional M-cones) in three families and between DMD and protan color blindness (absence of functional L-cones) in one family (Emery, 1966). Another study found a linkage between recombinant DMD and protan color blindness in one family (Greig, 1977). At that time, it was found that the *DMD* gene and the *opsin* genes involved in red-green color vision were located at two different loci on the X-chromosome (Zatz et al., 1974). Therefore, DMD itself is the cause of color vision abnormalities in DMD patients rather than a genetic interaction between the *DMD* and the *opsin* genes (Bonci et al., 2009).

Color vision thresholds have been more recently measured in DMD patients using the computerized Cambridge Color Test (CCT; Costa et al., 2007). The CCT determines color discrimination thresholds along different directions in the CIE 1976 color space (Regan et al., 1994). Visual stimuli are Landolt C rings with chromaticities that differ from the background. The subjects' task is to indicate the position gap of the Landolt C. The CCT can be reliably used to test young patients (Goulart et al., 2008), even patients with neurodevelopmental conditions (Zachi et al., 2017). DMD patients displayed color vision losses particularly in the red-green direction (i.e. involving L- and M-cones). In line with ERG data, a higher prevalence was found in patients with genetic alterations downstream of exon 30 (Costa et al., 2007). The altered cone-driven ERG responses observed in patients lacking Dp427, Dp260 and Dp140 (Barboni et al., 2013, 2016, 2020a) suggest a putative role for Dp140 in cones, which would be supported by detection of the Dp140 mRNA in these cells. However, a direct comparison with responses measured in

patients lacking only Dp427 and Dp260 has yet not been reported to strengthen this hypothesis.

Other psychophysical measurements included spatial and temporal contrast sensitivity tests using luminance and chromatic (red-green and blue-yellow) sinusoidal gratings as visual stimuli. Furthermore, luminance sinusoidal modulation of different temporal frequencies in Gabor patches was used. These measurements showed that DMD patients had general sensitivity losses to spatial and temporal achromatic contrasts, while showing more prominent losses to red-green than blue-yellow contrasts. In general, DMD patients with specific loss of Dp427 (upstream of exon 30) were less strongly affected (Costa et al., 2011). Contrast sensitivity was also measured to increments (On) and decrements (Off) achromatic checkerboards. Reduced contrast sensitivity was observed for contrast increments (Barboni et al., 2013). Due to the low number of participants, it was not possible to conclude if patients with and without functional Dp260 had different thresholds.

The identification of specific visual dysfunctions such as color thresholds, luminance, chromatic and temporal contrast sensitivity, can provide biomarkers of retinal dysfunctions. The assessment of visual losses as a function of a patient's genotype in DMD may assist in monitoring disease progression and possible future treatment effects. In addition, clinicians should be aware of visual impairments when developing rehabilitation programs and applying cognitive tests with visual patterns in DMD patients.

#### 6.6. Other ocular manifestations in DMD patients

DMD patients show a high prevalence of cataracts compared to age-matched healthy subjects. Dp71 is the major *DMD*-gene product in the fiber cells of the crystalline lens. Other dystrophin transcripts were also detected in the developing crystalline lens, surrounding the equatorial nuclei of primary lens fibers (Dp140) and throughout the lens fibers and the developing lens epithelium (Dp71 and isoforms) (Hildyard et al., 2020). Its absence has been associated with progressive cataract in Dp71-null as well as in *mdx*<sup>3Cv</sup> mice, however with a difference in age onset and opacity type (Fort et al., 2014; Karnam et al., 2021). This may not fully explain the higher cataract prevalence in DMD patients, since only a minority of patients hold genetic abnormalities that affect Dp71 (i.e. mutations downstream of exon 63). However, it must be considered that subcapsular opacities of the crystalline lens have also been reported in the Dp427-deficient *mdx* mouse (Kurihara et al., 1990) showing that dysfunctional Dp427 could also affect the crystalline lens of DMD patients. A complicating factor is that glucocorticoid therapy may result in an increased risk of developing cataract (Rice et al., 2018). Another clinical finding that is possibly associated with the medication is the increased macular pigmentation that has been reported in DMD patients (Sigesmund et al., 1994). One publication reported normal OCTs in DMD patients without secondary retinal diseases (Ricotti et al., 2016a).

Finally, a more severe ocular manifestation is sometimes found in DMD patients: the so-called Duchenne-associated proliferative retinopathy. At least nine cases of proliferative retinopathy caused by ocular ischemic events in DMD patients have been reported (Bucher et al., 2019; Fagan et al., 2012; Hahn et al., 2013; Kecik et al., 2021; Lin et al., 2012; Louie et al., 2004; Ober et al., 2006; Park et al., 2019; So et al., 2012). This could be secondary to medications or due to the advanced stages of cardiopulmonary failure causing hypoperfusion and hypoxia in the retina. However, dysfunction of the full-length dystrophin (Dp427), and likely of the smaller *Dmd* gene products (Ortiz et al., 2019), alter vascular structure and function, potentially triggering neovascularization, as recently reported in aging *mdx* mice (Bucher et al., 2019).

Table 3 compiles the demographics of DMD patients with proliferative retinopathy described in a series of clinical cases. The reported data include the age at which the retinopathy was diagnosed, the best-corrected visual acuity measured before treatment, type of treatment against the neovascularization, and the result of the treatment observed

**Table 3**

Summary of Duchenne-associated proliferative retinopathy clinical reports.

Reference	Age	Exon	VA RE	VA LE	Treatment	Outcome
Louie et al. (2004)	25	–	CF	20/70	Panretinal photocoagulation	Little effect on neovascular progression
Ober et al. (2006)	18	–	20/40	HM	Surgical intervention (vitrectomy)	Relatively stable VA (RE: 20/60)
Fagan et al. (2012)	23	–	20/1200	20/40	Anti-VEGF treatment	Regression of the neovascularization
Lin et al. (2012)	23	–	20/20	20/20	Panretinal photocoagulation	Regression of the neovascularization
So et al. (2012)	23	–	20/2000	HM	Surgical intervention (vitrectomy)	VA improvement (RE: 20/25)
Hahn et al. (2013)	23	–	20/20	20/20	Panretinal photocoagulation	Improvement to at least one year
Bucher et al. (2019)	21	3–7	CF	CF	Anti-VEGF treatment	Stabilized neovascularization
Park et al. (2019)	30	–	20/1000	CF	Surgical intervention (vitrectomy)	VA improvement (RE:20/125, LE:20/60)
Kecik et al. (2021)	28	–	LP	CF	Surgical intervention (vitrectomy)	No improvements

VA: Visual acuity, CF = counter finger, HM = hand movement, LP = light perception, RE = right eye, LE = left eye, Exon = position of the genetic alteration. – = genetic alteration not reported.

in the DMD patients. Based on these case reports, it can be concluded that the onset of proliferative retinopathy in DMD patients, with severely impaired visual acuity, is associated with an advanced stage of the disease, since all patients except one (Ober et al., 2006) were older than 20 years. Moreover, cardiopulmonary insufficiency may influence the onset of proliferative retinopathy, although in one clinical case the cardiac function was normal (Park et al., 2019). Overall, non-surgical treatment may be effective in some cases while surgical interventions may be necessary in advanced cases.

Probably, ocular ischemia as well as retinal inflammation are occasional events in DMD that require further investigation. As life expectancy increases in DMD patients with new treatments, cases of proliferative retinopathy could become more prevalent. These case reports suggest that DMD patients older than 20 years may have an increased risk for developing severe retinopathies and, therefore, require periodic ocular monitoring.

## 7. Neural bases of altered retinal physiology in dystrophin-deficient mouse models

Standard flash ERGs have been studied in most dystrophic mouse models holding distinct genetic mutations that prevent the expression of multiple dystrophins, i.e. the *mdx*, *mdx*<sup>2Cv</sup>, *mdx*<sup>3Cv</sup>, *mdx*<sup>4Cv</sup>, *mdx*<sup>5Cv</sup> and *mdx52* mice (Table 1 and Fig. 5 A). Retinal function is relatively preserved in the Dp427-deficient *mdx* (Bucher et al., 2019; Cibis et al., 1993; Pillers et al., 1999) and *mdx*<sup>5Cv</sup> (Pillers et al., 1999) mice, which

were therefore initially not considered to be appropriate models for studying DMD-related retinal abnormalities (Pillers et al., 1995). Possibly, the fact that these mice show normal expression of other retinal dystrophins may lead to a mild phenotype. However, a more recent study revealed more severe ERG alterations and specific age-related retinal dysfunctions in *mdx* mice, including increased retinal neovascularization in response to hypoxic stress (Bucher et al., 2019) that are relevant to the Duchenne-associated proliferative retinopathy, as described above. In this study, the young-adult Dp427-deficient *mdx* mice showed small reductions in the dark- and light-adapted flash and 30 Hz flicker ERG amplitudes (maximally by 23–26%), while the older *mdx* mice (>15 months old) showed a larger reduction in the amplitude of the ERG flash response.

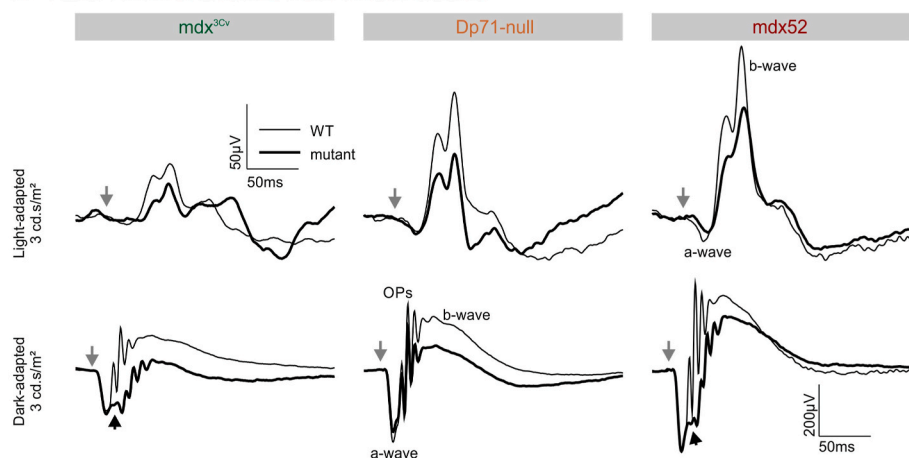
The *mdx*<sup>2Cv</sup> mouse model of DMD lacks Dp427 and Dp260 and shows more strongly affected ERGs compared to *mdx* and *mdx*<sup>5Cv</sup> mice (Pillers et al., 1999) where only Dp427 is affected. As mentioned above, this suggests that Dp260 is required for normal retinal function. However, more extensive studies of this model are still lacking.

The *mdx*<sup>3Cv</sup> mouse, which shows a drastic reduction of all dystrophins, appears to better mimic the human ERG abnormalities observed in DMD patients. As shown in Fig. 5 B, ERG responses measured in the *mdx*<sup>3Cv</sup> mouse (all dystrophins affected) display a large reduction of dark-adapted ERG b-waves (Pillers et al., 1995, 1999; Tsai et al., 2016). A comparison of the ERG phenotypes of *mdx*<sup>3Cv</sup> mice (Tsai et al., 2016), *mdx52* mice (Barboni et al., 2021b) where only Dp71 is spared, and Dp71-null mice that only lacks Dp71 is shown in Fig. 5 B. We found that

### A Postition of mutations in DMD mouse models



### B Flash-ERGs in different DMD mouse models

**Fig. 5. ERG abnormalities in DMD mouse models.**

(A) Position of the different mouse mutations in the DMD gene. ERG responses to standard ISCEV light-adapted (top traces) and dark-adapted (bottom traces) flashes are shown for *mdx*<sup>3Cv</sup> mice (expression of all dystrophins is drastically reduced, with only minimal residual expression), Dp71-null mice (selective loss of Dp71) and *mdx52* mice (lacking all dystrophins but Dp71). Thin traces show responses of WT littermate mice, while the thick traces show ERGs of the dystrophic mouse models. ERG responses were generally reduced in amplitude in the *mdx*<sup>3Cv</sup> study because the mice were older than in the other two studies. All three mouse models showed altered ERGs compared to their WT littermates. A shoulder was consistently observed on the ascending limb of the b-wave in *mdx*<sup>3Cv</sup> and *mdx52* mice (black arrows in bottom panel), but not in WT mice. Traces from Barboni et al. (2021b), 2020b; Tsai et al. (2016).

the *mdx*<sup>3Cv</sup> mouse displayed a complex ERG phenotype (Tsai et al., 2016), resembling that observed in DMD patients with genetic alterations affecting more than one dystrophin. However, this model has several limitations: (i) it was reported that *mdx*<sup>3Cv</sup> mice may display residual expression of dystrophins (Daloz et al., 2001; Li et al., 2008, 2010); (ii) it represents a rare mutation in patients; (iii) its mutation in intron 65 cannot be suppressed by exon-skipping strategies without affecting critical functional domains of the protein and this model is therefore not suitable for investigating current molecular therapies.

However, the strong ERG phenotype in *mdx*<sup>3Cv</sup> mice, also compared to the findings in the *mdx52* mouse, suggests that the absence of Dp71 is a major aggravating factor. Dp71 is the shortest, but most abundant dystrophin in the retina and its absence has been associated with increased blood-retina barrier permeability, inflammation, capillary degeneration and retinal edema, in addition to altered water homeostasis and delayed potassium buffering (Tadayoni et al., 2012). Using the Dp71-null mouse model, it was shown that a selective loss of Dp71 alters retinal structure and function (Cia et al., 2014, p. 200; Daloz et al., 2003; El Mathari et al., 2015; Fort et al., 2008; Sene et al., 2009). We have re-evaluated retinal electrophysiology in this mouse model using an extensive full-field ERG repertoire that revealed reduced b-waves in dark- and light-adapted flash ERGs and smaller response amplitudes to photopic rapid-On sawtooth modulation and to sine-wave stimuli (Barboni et al. 2020). This suggests mild but multiple effects of Dp71 loss on retinal function.

Because Dp71 expression have not been demonstrated in retinal neurons, these results suggest that the absence of Dp71 in Müller glial cells (MGCs) may have a direct impact on the ERG. Amongst multiple functions, MGCs are responsible for the extracellular ionic balance of the retina (Newman, 1985; Newman and Zahs, 1998; Reichenbach et al., 1993), influencing the generation of the ERG b-wave (Newman and Odette, 1984). In the absence of Dp71, Kir4.1 and the AQP4 channels are redistributed over the entire surface of the MGCs, instead of being concentrated in their endfeet and in the extensions surrounding blood vessels (Connors and Kofuji, 2002; Daloz et al., 2003; Fort et al., 2008). Furthermore, AQP4 is downregulated. As a result, ionic retinal currents are not properly aligned, thus explaining why both dark- and light-adapted ERG b-waves are affected in Dp71-null mice (Barboni et al., 2020b). This notion is partly supported by the observation that ERG changes occur in human patients with mutations in the KCNJ10 gene that encodes Kir4.1 (Thompson et al., 2011).

The *mdx52* model also appears to be an attractive model for most human DMD-related retinal disorders, as the position of the deletion (exon 52) corresponds to a hotspot region involved in about 60% of the human DMD population, and because it can be used for exon-skipping therapeutic strategies (Akpulat et al., 2018; Aupy et al., 2020). This mouse model, alike *mdx*<sup>4Cv</sup> mice, lacks Dp427, Dp260, and Dp140, but still expresses Dp71. The ERG phenotype of *mdx52* mice includes key features observed in DMD patients. The flash ERG in *mdx52* mice was first characterized by delayed dark-adapted b-waves (Kameya et al., 1997). We recently studied the ERG defects in *mdx52* mice in more detail (Fig. 5 B). The study revealed reduced amplitudes and delayed peak times of the dark-adapted a-wave, b-wave, and oscillatory potentials (OPs). Light-adapted flash ERGs showed diminished amplitudes but normal peak times. In addition, reduced responses mediated by On- and Off-sawtooth stimuli in both mesopic and photopic conditions were observed. The responses to photopic sine-wave flicker were also reduced in amplitude but their phases were not altered. These results suggest that both photoreceptor types and bipolar cell/inner retina functions are altered. The *mdx52* mice also showed reduced contrast sensitivities measured with the optokinetic reflex (Barboni et al., 2021b). These findings suggest that the *mdx52* model may have a strong translational value to study the molecular and cellular bases of altered photoreceptor-to-bipolar cell transmission in DMD. As for patients with distal mutations downstream of exon 30, the cone-driven ERG defects displayed by *mdx52* mice suggest a putative role for Dp140 in cones, but

direct comparison with responses measured in mice lacking only Dp427 and/or Dp260 is still missing to reach a firm conclusion on the specific contribution of Dp140 to retinal function.

The precise mechanisms underlying the complex pattern of ERG defects observed in *mdx52* mice are still unknown, and likely involves dysfunctions related to all the missing dystrophins. One major and general mechanism may relate to the alteration of the molecular bridge linking dystroglycan (at photoreceptor level) to GPR179 (at On-bipolar cell level), which may underlie the changes in the b-wave amplitude and peak times. Indeed, alterations in GPR179 expression can modify the localization of the GTPase accelerators RGS7 and RGS11 involved in mGluR6 signaling in the bipolar cell, and this may likely affect the kinetics and amplitude of the ERG b-wave (Cao et al., 2012). A similar but milder mislocalisation of RGS7 and RGS11 has been observed in *mdx*<sup>4Cv</sup> and *mdx*<sup>3Cv</sup> mice (Orlandi et al., 2018). This suggests that in these models, and possibly in DMD patients with mutations downstream of exon 30, the On and Off pathways are no longer processing visual information at the same speed (DeVries et al., 2006). In both the *Pikachurin*<sup>-/-</sup> and *Dystroglycan* cKO mice, the tips of rod bipolar cell dendrites no longer invaginate into rod photoreceptor terminals (Omori et al., 2012; Sato et al., 2008). The same is probably true for On-bipolar cell dendrites and cone pedicles. This should result in a slower synaptic transmission between photoreceptors and On-bipolar cells. However, the ultrastructure of the rod spherules and cone pedicles and their implications for the ERG in DMD mouse models has not been examined in detail. These hypotheses could set the ground for future studies aimed at deciphering the neurobiology of DMD.

## 8. Rescuing structural and functional retinal phenotype

Although dystrophinopathies have been studied for many decades, unfortunately, they are currently still incurable. The available pharmacological methods attempt to relieve the symptoms caused by the muscle dysfunction while cardiorespiratory rehabilitation is used to prolong life expectancy (Bladen et al., 2015; Koeks et al., 2017). Several modern genetic tools are under development to rescue dystrophin expression so that some muscular function can be maintained or restored, using either correction strategies based on exon skipping or on AAV-mediated replacement strategies. Perspectives of bench to bedside gene therapy translation still pose many challenges and hurdles concerning delivery, toxicity, adaptation to distinct mutations, and crossing of the blood brain barrier, particularly when intervention are undertaken postnatally. To bring gene therapy closer to whole-body delivery for full treatment of DMD patients, scientists are facing challenges to adapt these molecular tools to cross central nervous system barriers and to target brain and retinal tissues. However, several studies from our group provided encouraging results, showing the possibility to select specific AAV-vector serotypes that can cross retinal barriers and target specific retinal cell types, or by using antisense oligonucleotides with modified chemistries to facilitate the crossing of the vascular barriers to perform exon-skipping rescue strategies (Vaillend et al., 2019).

Dystrophins are modular proteins that can endure removal of some exons to restore an opening reading frame in partially deleted dystrophin mRNAs. This can give rise to truncated but semi-functional forms. Our studies showed the possibility to rescue expression of brain dystrophin by bypassing the *mdx* mutation with splice-switching strategies (exon-skipping), which allowed partial re-expression of a slightly truncated but functional dystrophin causing functional improvements (Goyenvalle et al., 2015; Vaillend et al., 2010). It is likely that these approaches can also be efficient to restore the function of retinal dystrophins.

The extensive full-field ERG repertoire that we have used to evaluate retinal dysfunction in *mdx* mouse lines provides relevant outcome measures that may be used as biomarkers of treatment efficacy. However, a full characterization of specific retinal alterations across distinct mutation profiles is required, in order to characterize optimal



translational models for preclinical studies. Translation of molecular therapy approaches to compensate retinal alterations also requires determining whether ERG alterations in dystrophin-deficient mouse models are restored after these treatments. For the first time, we demonstrated the possibility to rescue retinal anomalies in the Dp71-null mouse by gene therapy. This was obtained following intra-vitreous injections of an SHh10-GFP AAV vector engineered to transduce Müller glial cells (MGCs) specifically and containing the complete coding sequence of Dp71 (Vacca et al., 2014). We showed that this construct is efficient to induce a strong and specific re-expression of Dp71 in MGCs, which encompassed the whole retina of treated Dp71-null mice. This ectopic re-expression of Dp71 was correctly localized in the inner limiting membrane, at the glial-vascular interface, and was accompanied by a relocalization of AQP4 and Kir4.1 channels. At the functional level, the blood-retina barrier permeability of Dp71-null mice was normalized (Vacca et al., 2016). Finally, in a follow-up study, we showed that this therapeutic approach enables full functional recovery of the affected ERG parameters in Dp71-null mice (Barboni et al., 2020b), including the On-bipolar cell dependent b-wave amplitudes and the responses to sawtooth and sine-wave stimuli. It seems unlikely that the re-expression of Dp71 in MGCs of the adult retina can restore early morphologic alterations occurring during development. We therefore concluded that the restoration of Kir4.1 and AQP4 clustering at MGCs in Dp71-null mice was the main mechanism to explain the ERG recovery. Importantly, this pointed to a modulatory role of MGCs in ERG b-wave generation.

This attempt to rescue retinal alterations following restoration of Dp71 expression demonstrates that DMD-related ERG defects may well respond to strategies based on postnatal molecular therapy. This is encouraging for the development of genetic therapies aiming at alleviating the central comorbidities associated with DMD. Because both cognitive and visual symptoms show a typical non-progressive profile from childhood to early adulthood, they could be reliably used as biomarkers for testing the efficacy of such therapies. Another issue to be considered is that increased VEGF expression and retinal inflammation, that are observed in Dp71-null mice (El Mathari et al., 2015), are not observed in *mdx*<sup>3Cv</sup> mice, suggesting that low levels of Dp71 expression could be sufficient to suppress inflammation and the ocular ischemic events (Rendon et al., unpublished data). Therefore, future systemic gene therapies that only partially restore the expression of retinal dystrophins may be sufficient to improve retinal function and prevent acute ocular ischemic events. Moreover, our construct enabled rescue of the full-length Dp71d isoform, suggesting that rescuing all Dp71 isoforms normally expressed in retina is not required to functionally compensate the retinal defects. These data suggest that DMD mouse models may help to better understand the molecular and cellular bases of Duchenne-associated proliferative retinopathy and to test genetic treatments.

## 9. Future perspectives

### 9.1. Expression of retinal dystrophins

The abnormal ERGs observed in DMD patients and DMD mouse models indicate that the functional deficits are mainly caused by the dysfunction of dystrophins at the photoreceptor (rod and cone) synapses. This agrees with the finding that Dp427, Dp260, and Dp140 are expressed in the outer plexiform layer (OPL) of the retina. To our knowledge, no hypothesis has been proposed to explain why three different dystrophins are expressed in photoreceptors, nor why the Dp427/Dp260 ratio seems to be different in cones and rods (Wersinger et al., 2011). The relative expression level of each dystrophin in the retina could reflect expression in distinct subpopulations of specific cell types and may vary depending on the cell stage of differentiation/maturation and/or in response to activity-dependent processes, as previously proposed for some brain cells (Aranmolate et al.,

2017; García-Cruz et al., 2022; Hildyard et al., 2020). It remains to be investigated whether distinct dystrophins are localized in distinct subtypes of rods and cones with specific molecular signatures, or in separate subcellular domains in mature photoreceptors.

A recent comparative atlas of human retinal single-cell transcriptomes detected DMD mRNAs in rods and cones, in different subtypes of On-bipolar cells, and, more surprisingly, in different subtypes of Off-bipolar cells expressing specific molecular signatures (Cowan et al., 2020). As known from mouse studies, this suggests that dystrophins are expressed in a range of cell types and subtypes in the human retina. It also highlights that next generation sequencing methods may uncover the presence of a large variety of new cell subtypes in the retina. Whether distinct dystrophin isoforms are expressed in separate cell subtypes or cell subpopulations remains to be elucidated, as the standard methods based on sequencing from the 3' polyadenylated tail do not allow identification of full-length mRNAs and subtype-specific isoforms. Moreover, whether all dystrophin mRNAs and splice variants are actually translated into proteins also remains a challenging question, as many of the currently available antibodies are pan-specific due to the high structural sequence homology amongst dystrophins and their alternatively spliced isoforms. Future investigations with more specific antibodies, along with high resolution confocal or electron microscopy techniques, on animal tissues or organoids, may help to refine the expression profiles of dystrophins in distinct cell subtypes and/or functional subcellular domains, as well as their putative differential expression during retinal development and maturation.

The recent and future developments in multi-omics and *in vitro/ex vivo* cellular biology may likely open new avenues and offer new tools to specify the localization and cellular function of dystrophins, which may be guided by two main objectives:

- To develop multi-omics analyses in organoids, purified-cell cultures and single cells, to decipher expression of all dystrophins and splice variants in distinct cell subpopulation and during distinct stages of retinal development.
- To develop new antibodies and proteomic approaches to better decipher dystrophin interactome in distinct retinal cell types.

### 9.2. ERG phenotypes in DMD patients

ERG defects in DMD patients point to abnormalities in the signal transmission between photoreceptors and mainly depolarizing On-bipolar cells. Since the rod bipolar cells are all of the On-type, retinal processing is particularly affected under scotopic conditions (Barboni et al., 2021a, 2013; Cibis et al., 1993; Cibis and Fitzgerald, 2001; De Becker et al., 1994; Fitzgerald et al., 1994; Girlanda et al., 1997; Ino-ue et al., 1997; Jensen et al., 1995; Pascual et al., 1998; Pillers et al., 1999; Pillers et al., 1993; Ricotti et al., 2016a; Sigismund et al., 1994; Tremblay et al., 1994; Ulgenalp et al., 2002). Despite the consistent dark-adapted ERG alterations in DMD patients, some studies using psychophysical tests showed normal dark adaptation in patients with DMD. In one study, the tests were performed with white light flashes, presumably, during 40 min of dark adaptation after a 5-min bleach (to 600 cd/m<sup>2</sup>) in 3 patients with the clinical DMD diagnosis (without genetic confirmation), one of them displaying normal ERGs (Tremblay et al., 1994). A second study reported normal dark adaptation in patients clinically diagnosed with DMD or BMD (Jensen et al., 1995). Unfortunately, it is unclear if the measured thresholds in these studies were mediated by cone or by rod activity and which dystrophins were affected in each patient. More recently, our group showed that psychophysical dark-adapted rod mediated visual thresholds are affected in genetically confirmed DMD patients with genetic mutations downstream of exon 30, where at least Dp260 is affected in addition to Dp427 (Barboni et al., 2021a). These findings are in agreement with histological data showing dystrophins localized in juxtaposition with mGluR6 in invaginating synapses of both rods and cones (Blank et al., 1999; Kameya et al., 1997;



Ueda et al., 1995; Wersinger et al., 2011), where signals to On-bipolar cells are transmitted (Regus-Leidig and Brandstätter, 2012; Sterling and Matthews, 2005). Under mesopic conditions, rod signals are mainly transmitted via the cones through gap junctions (Völgyi et al., 2004). It therefore can be expected that under mesopic conditions, the responses are less affected than under scotopic condition. More data on the influence of mean luminance and the state of adaption on the ERG changes may bring insights into pathophysiological mechanisms.

The genotype-ERG phenotype relationships in DMD are still unclear, yet more in-depth studies could shed new light on the specific cellular functions of retinal dystrophins. It has been established that DMD patients with genetic mutations downstream of exon 30, lacking both Dp427 and the retina-specific Dp260 dystrophin, are much more affected than DMD patients with mutations upstream of exon 30 lacking only Dp427 (Barboni et al., 2021a; Ino-ue et al., 1997; Pillers et al., 1999; Ricotti et al., 2016a; Ulgenalp et al., 2002). However, groups of DMD patients with mutations downstream of exon 30 encompass a variety of mutation profiles that may differentially impede the expression of Dp260, Dp140 and Dp71. If the cumulative loss of several dystrophins obviously induces an ERG phenotype, future studies detailing the specificities of the ERG phenotype in distinct subgroups of patients is required to advance our understanding regarding the function of each DMD-gene product. Hence, phenotypes of patients lacking Dp427 and Dp260 (mutation between exons 30 and 44) should be compared with the phenotype of patients with more distal mutations that additionally affect expression of Dp140 (between exons 45 and 62) and Dp71 (downstream of exon 62). Regarding the effects of a cumulative loss of all dystrophins including Dp71 on human ERGs, only two DMD patients have been described so far (Ricotti et al., 2016a), to the best of our knowledge. These patients displayed a greater reduction of ERG b-wave amplitudes than DMD patients with distal mutations that preserve Dp71 expression. However, the small number of clinical cases does not allow to establish a definitive conclusion. Although quite infrequent, cases of patients with a selective dysfunction of Dp71 would also be informative to understand the specific function of Dp71 (de Brouwer et al., 2014).

The following questions are relevant to further our understanding of DMD neurobiology and to develop specific therapeutic approaches to alleviate central nervous system dysfunctions in DMD:

- How much of the ERG alterations observed in DMD patients results from the sole loss of Dp260 and how much depends on the cumulative loss of other dystrophins? Is Dp140 required for normal retinal function? This would require larger cohorts of patients for systematic and more powerful comparisons of several subgroups of patients with differential loss of the distinct dystrophins. This type of question might also be addressed with rare case studies of BMD patients with in-frame mutations selectively affecting the Dp260 or Dp140 promoter (or its translation start site in exon 51 for Dp140).

Future patient studies should consider the use of extended ISCEV ERG protocols providing additional characterization of the rod (Johnson et al., 2019) and cone (McCulloch et al., 2019) system functions, as well as of different post-receptoral pathways. However, it is recommendable to implement the following experimental protocols:

- Sawtooth stimuli to solicit On- and Off-pathways (Barboni et al., 2013).
- Photopic negative response (PhNR) in the flash ERG (Frishman, 2006) or the pattern reversal ERG (Bach and Hoffmann, 2006) to give information about the function of retinal ganglion cells.
- Heterochromatic sine waves for studying luminance and chromatic pathways (Kremers et al., 2010), which may provide information about how post-receptoral (chromatic and luminance) mechanisms are affected.
- Luminance sine wave stimulation at different temporal frequencies, which may also provide information about different post-receptoral

(sinusoidal and transient) mechanisms (Pangeni et al., 2010) and about On-Off asymmetries (Kondo and Sieving, 2001).

- Rod- and cone-isolating stimuli using silent substitution techniques that enable to study photoreceptor driven signals independent of the state of adaptation (Kremers, 2003). Thus, the influence of DMD on adaptation could be studied independently. We have shown recently that dynamics of adaptation may be affected differently in rod- and cone-driven signals by DMD (Barboni et al., 2021a).
- Finally, the use of white noise stimuli may be interesting for efficient characterization of ERG responses in patients because many of the above characteristics can be obtained within a limited recording time and because the stimuli more closely resemble the properties of natural scenes and are more convenient for the patients (Kremers et al., 2022; Zele et al., 2017).

### 9.3. Relevance of animal models' phenotypes to the human condition

The genotype-phenotype relationships underlying ERG defects in DMD have been addressed in mouse models holding distinct mutations in the *Dmd* gene (Pillers et al., 1999). Although ERG analyses in DMD mouse models enable to apprehend the role of the distinct dystrophins, there are still many caveats that may require development of new models and systematic comparisons with an extended repertoire of ERG stimulation protocols. The selective role of Dp427 has been studied in the *mdx* mouse model (Bucher et al., 2019; Cibis et al., 1993; Pillers et al., 1999), and that of Dp71 using the Dp71-null mouse (Barboni et al., 2020b; Cia et al., 2014; Dalloz et al., 2003; Fort et al., 2008; Giocanti-Auregan et al., 2016; Vacca et al., 2014). The *mdx*<sup>2Cv</sup> mouse model, lacking Dp427 and Dp260, has not been characterized in as much detail as the *mdx*52 mouse model lacking Dp427, Dp260 and Dp140, in which robust ERG alterations were observed even in young adult mice (Barboni et al., 2021b). It has been suggested that *mdx*<sup>4Cv</sup> mice, that also lack Dp427, Dp260 and Dp140, are similar to *mdx*<sup>2Cv</sup> mice regarding the ERG phenotype (Pillers et al., 1999), but this warrants further investigations. Models with a selective loss of Dp260 or Dp140 are not yet available but could be pivotal to precisely characterize the cellular and molecular bases of retinal and visual alterations in DMD/BMD.

The impact of a cumulative loss of all dystrophins has been addressed using the *mdx*<sup>3Cv</sup> mouse (Pillers et al., 1995, 1999; Tsai et al., 2016). Because the selective loss of Dp71 in Dp71-null mice affects the ERG, mice lacking all dystrophins are expected to present a more severe phenotype than the other mouse models. The severe ERG phenotype characterized by a negative dark-adapted ERG b-wave largely reported in DMD patients was also found in *mdx*<sup>3Cv</sup> (Tsai et al., 2016). The relevance of the *mdx*<sup>3Cv</sup> model for comparisons with patient data has been, however, debated and, intriguingly, a severe phenotype was also reported in *mdx*52 mice where Dp71 is spared (Barboni et al., 2021b). The investigation of other models with genetic alterations leading to a full loss of all dystrophins, such as the *mdx*- $\beta$ -geo or the *Dmd*-null mice, should be considered in future studies.

Although mouse models enable advances in this field of research, their characterization is still incomplete, and the seminal results warrant more investigations and more robust comparisons with the data obtained from human subjects. For example, a selective Dp427 loss mildly affects ERGs in young-adult *mdx* mice, in line with the mild or absent phenotype in DMD patients with a specific Dp427 mutation (Barboni et al., 2021a; Ricotti et al., 2016a). However, recent reports revealed the repercussions of Dp427 loss to mouse retinal homeostasis and vascularization: i) increased retinal neovascularization in response to hypoxic stress during aging (Bucher et al., 2019); II) altered shaping of specific steps of retinal differentiation and maturation (Persiconi et al., 2020); and iii) cell death, impaired autophagic processes and altered photoreceptor-synapse architecture (Catalani et al., 2021). These are clinically very relevant findings since Dp427 is affected in all DMD patients and might underlie the proliferative neovascularization in aging DMD retinas. These dysfunctional cellular processes need to be further

specified in future studies and may benefit from the use of the diverse animal models that are currently available to study DMD pathophysiology. Moreover, the impact of aging and hypoxia has not been addressed in DMD patients, but this might also be relevant for BMD patients whose life expectancy is currently longer.

Mouse models might not recapitulate the full repertoire of alterations associated with DMD in humans, since ERG differences are already present between human and mouse in healthy conditions. Human and mouse dark-adapted (rod-driven) ERGs share similar features, such as a b-wave that is larger than the a-wave and the presence of OPs. However, OPs are generally much larger in mice. Furthermore, cone-driven ERG responses can be quite different, and the cone types in the mouse retina are different from the human cone types. Mouse and human cone-driven ERGs may have intrinsic differences. Using cone isolating sinusoidal stimuli, it was found that mouse M-cone-driven responses resemble mouse and human S-cone-driven responses (Mowat et al., 2019). Human L- and M-cone driven responses are quite different from human S-cone driven responses. This indicates that mouse M-cones may have characteristics that are more like human S-cones than human M-cones. This notion is also supported by the finding that in mice many cones express both S- and M-pigment, suggesting that cones in mice are uniform (Applebury et al., 2000) and lack the functional distinction between human L- and M-cones on the one hand and human S-cones on the other hand.

Another point to consider is that ERGs elicited by rapid-Off modulation as well as sine-wave luminance modulation display quite different waveforms between species. They could be differently affected by dystrophins' dysfunctions. A detailed comparison of ERGs from DMD patients and DMD mouse models is required to confirm if the post-receptoral dysfunctions found in DMD patients (asymmetric On-Off responses) are comparable to those reported in mouse models of DMD (Barboni et al., 2020b, 2021b; Tsai et al., 2016).

Despite such putative discrepancies between species, the reduced dark-adapted ERG b-waves are typical alterations in both DMD patients and DMD mouse models, and the mouse models allow more detailed physiological and structural studies of the retina. Mouse models therefore remain invaluable tools to target the cellular and molecular bases of dystrophin functions and dysfunctions in the retina. Moreover, mouse models are also relevant for the preclinical evaluation of therapeutic compounds. Our recent studies on the rescue of Dp71 expression in the retinae of Dp71-null mice by gene therapy (Barboni et al., 2020b; Vacca et al., 2016) suggest potential benefits of these therapeutic strategies for patients. This successful first attempt to rescue dystrophin expression in the retina using gene therapy is promising and emphasizes that the retina is sensitive to molecular therapies targeting central nervous system tissues. Future challenges will be to adapt molecular tools to envisage re-expression of other missing retinal dystrophins in DMD mouse models and thereby assess the molecular and cellular mechanisms by which postnatal rescue of dystrophins may reverse central nervous system functional deficits.

Non-mammalian DMD models such as Zebrafish and *Drosophila* may be considered in future investigations of the differential functions specific dystrophins play during embryonic and early-stage development. They may also contribute to the studies of diseases progression and therapeutic interventions. Nevertheless, limitations of these models such as the evolutionary distance to humans and cone-versus rod-dominated retinas may be considered. Alternatively, or additionally, future studies should take advantage of the diversity of mammalian models, such as the pig (Stirm et al., 2022), rat (Caudal et al., 2020), dog (Zaynitdinova et al., 2021) and humanized mouse models (Aartsma-Rus and van Putten, 2019) to better detail DMD pathophysiology and decipher relevant outcome measures for preclinical assessment of therapeutic strategies.

In summary, animal models may greatly increase our understanding of the mechanisms underlying retinal and visual dysfunctions and their relevance to the clinical condition. These may include:

- To use an extended repertoire of ERG stimulations to solicit distinct cellular pathways, as recommended for patients' studies, and reappraise comparisons of mouse models with distinct genotypes.
- To develop new mouse models with selective loss of specific dystrophins which retinal function still needs to be specified (Dp260, Dp140, Dp116).
- To take advantage of the diversity of DMD animal models, from non-mammalian to mammalian and humanized-mammalian models. Their specificities may be relevant to address specific developmental, pathophysiological or preclinical issues, and will help to circumvent discrepancies between animal species and human condition.
- To address the susceptibility of the dystrophin-deficient retina to environmental factors such as aging and hypoxia, depending on the genotype and affected dystrophin, and to investigate the mechanisms by which they may influence retinal morphology and physiology. This may include analysis of ERG parameters and their pharmacological modulation in acute retinal sections.
- To select relevant and translational outcome measures of the pathology, which could then be used as key functional assessment tools to address the putative reversibility of the phenotypes (physiological, morphological) using postnatal interventions based on pharmacological, molecular and gene therapies. If such pathophysiological markers constitute relevant signature of CNS dysfunctions depending on the genotype in DMD, they will also have a predictive value to design and test therapeutic strategies targeting brain tissues.

#### 9.4. Other clinical considerations

DMD patients are at higher risk of developing cataract and proliferative retinopathy, sometimes as a side effect of long-term glucocorticoid medications (Rice et al., 2018) or due to secondary effect of advanced cardiorespiratory dysfunctions. This may mask a direct effect of DMD-gene mutations on the crystalline lens and the retina. The associations between DMD status and the onset of cataract and proliferative retinopathy needs to be studied with follow-up fundus examinations and OCTs in DMD patients and, very importantly, in BMD patients showing milder muscular symptoms with longer life expectancy.

Dp427 (Bucher et al., 2019) as well as Dp71 (Hildyard et al., 2020) have recently been shown to influence retinal and lens vascularization. Therefore, DMD patients lacking Dp71, in addition to all other dystrophins, might be at greater risk of severe ocular diseases. Regardless of the use of medication and the presence of cardiorespiratory dysfunction, ophthalmological examinations should be systematically prescribed to DMD patients by their health providers, as emphasized by a series of proliferative retinopathy causing severe visual losses in DMD patients.

The negative dark-adapted ERG b-wave that is highly prevalent in DMD patients is also found in other retinal diseases (Jiang and Mahroo, 2021), often indicating a selective involvement of the On-pathway (Pardue and Peachey, 2014). For instance, the negative dark-adapted ERGs measured in DMD patients are reminiscent of those obtained in patients with congenital stationary night blindness -CSNB- (Barnes et al., 2002). However, the light-adapted ERG responses differ between DMD and CSNB patients of the complete type (Cibis and Fitzgerald, 2001, p. 20101; Tremblay et al., 1994). In DMD patients the light-adapted (standard ISCEV) flash response has been consistently reported as normal or slightly affected (Barboni et al., 2021a; Cibis and Fitzgerald, 2001; De Becker et al., 1994; Ricotti et al., 2016a; Sigesmund et al., 1994; Tremblay et al., 1994). In contrast, in patients with CSNB of the complete type (cCSNB), the light-adapted responses have a characteristic "square wave" appearance, because of the absence of early oscillatory potentials (Cibis and Fitzgerald, 2001; Lachapelle et al., 1983; Tremblay et al., 1994). Moreover, cone-driven (standard ISCEV) flicker response is normal in DMD patients while it is subnormal to nearly absent in patients with CSNB (Tremblay et al., 1994). In future investigations, the application of alternative ERG protocols allowing to measure specific post-receptoral mechanisms, as discussed above, may

provide additional cues to compare ERGs from these two patient groups. This may provide additional insights in their pathophysiology.

Finally, information concerning visual performance in DMD patients is scarce because clinical investigations rely on the Snellen visual acuity test which is usually normal in DMD patients without secondary ocular diseases such as cataract or proliferative retinopathy (De Becker et al., 1994; Sigesmund et al., 1994). This is likely because the detection of supra-threshold stimuli is not affected by DMD. However, procedures in which threshold contrasts and sensitivities are determined are affected in DMD patients (Costa et al., 2011). We have recently demonstrated that the *mdx52* mouse showed normal optomotor responses to black and white reversing gratings at high achromatic contrast (100%), but when contrast level was decreased to 50%, sensitivity was reduced compared to WT littermates (Barboni et al., 2021b). In DMD patients, we showed that color vision thresholds are also affected (Costa et al., 2007). This is likely because of a dysfunction in the cone-opponent (parvocellular) pathway (Barboni et al., 2016).

Testing these clinical features is unfortunately quite infrequent, but the current data described above suggest the following recommendations for future clinical research in DMD/BMD:

- To monitor the onset of cataract and proliferative retinopathy with follow-up fundus examinations and OCTs of the retina in both DMD and BMD patients.
- To design alternative ERG protocols to get insights regarding the commonalities and discrepancies between CSNB and DMD pathologies.
- To develop or apply appropriate visual and psychophysical tests to better analyze the nature and severity of deficits related to sub-threshold contrast sensitivity and color vision in distinct genotypes.

### 9.5. Conclusions

Despite compelling evidence that dystrophins play roles in retinal physiology, and that the loss of distinct dystrophins in DMD induces a reliable retinal phenotype, our understanding of the specific cellular mechanisms that depend on dystrophins' functions is still at its infancy. In this review we have detailed the state-of-the-art knowledge on retinal dystrophins expression and on ERG and visual defects associated with DMD, based on the current knowledge.

Abnormal dark-adapted (rod-dominated) ERGs and On/Off asymmetric photopic (cone) ERG responses are highly frequent in DMD patients and consistently described in mouse models of DMD. The ERG profile of alterations indicates that the functional deficits caused by *DMD/Dmd* gene mutations may originate at the rod and cone synapses. In addition, cataract and retinal vasculopathy have been described in DMD patients and mouse models of DMD. Data from our and other groups support the notion that Dp260 is required for normal retinal function in both mice and in humans. However, why three distinct dystrophins (Dp427, Dp260 and Dp140) are expressed in the OPL remains unknown. Dp71, and likely its isoforms, is pivotal for the homeostatic and vascular integrity of the retina. Future investigations may consider more precisely defining the sites of dystrophins expression in the retina and the deep phenotyping of DMD patients with different types of genetic alterations.

Based on the points raised above, we propose a general hypothesis to guide future investigations. Considering that Dp427 and Dp260 expression and functions in the OPL are likely different, we hypothesize that Dp427 plays functional roles mainly in the cone system that could benefit from compensatory mechanisms. For instance, preserved Off pathways providing the visual inputs in the cone system, preventing light-adapted ERG dysfunctions in *mdx* mice and in DMD patients with genetic alterations upstream of exon 30 and lacking only Dp427. Dp260, on the other hand, would be required for proper functioning of the rod system without the opportunity for such a parallel compensation. Dp140 is important for establishing the synapses between photoreceptors and

bipolar cells during embryogenesis and/or early stages of neurodevelopment, as it has been proposed for the brain, but perhaps has only minor influence on mature function. Possibly, the retinopathy caused by DMD is stationary or of slow progression, similar to CSNB. The severe cases of proliferative retinopathy may be the secondary effects of cardiorespiratory dysfunction. These systemic changes associated with severe retinal impairment are the main targets of current therapeutic interventions. Therefore, the ophthalmological evaluation is pivotal in clinical trials aimed at rescuing muscular and cardiac functions in DMD patients.

A more complete knowledge regarding dystrophins' functions in the retina may be beneficial for pre-clinical and clinical trials. This will help to test the efficacy of upcoming gene therapies designed to rescue muscle function but that may also be able to cross the vascular barriers to rescue dystrophin expression in the central nervous system. The corrective interventions aiming to rescue dystrophins expression in the central nervous system are usually more challenging than for muscle tissues. They may benefit from the results of studies on retina phenotypes, which may help the design of efficient tools to guarantee the appropriate high-level rescue of specific retinal dystrophins that are crucial in the mature human retina. Possibly, the ERG can be used as a sensitive marker for DMD-related retinal dysfunction and therapies.

In the present review, we have discussed remaining caveats and uncertainties in our understanding of the function of retinal dystrophins. This led us to suggest future directions for advancing research in the area of DMD and the retina. A solution for these issues would bring a great potential for developing therapeutic approaches that target various associated CNS dysfunctions caused by cell-specific dystrophin alterations.

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### Declaration of competing interest

The authors declare no commercial relationships.



## Data availability

Data will be made available on request.

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