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What is the ocular phenotype associated with a single exon 78 deletion in Duchenne muscular dystrophy?

Tuy Nga Brignol¹ · Dominique Mornet² · Cecilia Montañez³ · Dora Fix Ventura⁴ · Cyrille Vaillend⁵ · Alvaro Rendón⁶

To the Editor:

We have read with great interest the Brief Communication reporting for the first time a clinical and histopathological description related to a single exon 78 deletion in Duchenne muscular dystrophy (DMD) gene. The 13-year-old male patient suffered from myalgia after exertion, with persistent increase of serum creatine kinase. Muscle fibers morphology and architecture were minimally affected. Height and weight were above 70th percentile. Intellectual functions were normal [1].

In the discussion, the authors quoted a study about abnormal splicing of DMD exon 78 in dystrophic muscles in myotonic dystrophy type 1 (DM1). According to this study, during muscle development, the switch from embryonic to adult isoforms of dystrophin involved coordinated alternative splicing of two regions of the DMD gene: exons 71–74 and exon 78. Experimental abnormal splicing switch compromised muscle development, and muscle fiber maintenance.

These findings correlated with abnormalities described in skeletal muscle biopsies of DM1 patients.

In addition, we would like to bring the authors' attention to a study published in 2018 [2]. It shows that in adult mouse brain and retina, different dystrophin Dp71 isoforms were produced by alternative splicing of exons 71–74 and 78, being the isoforms differentially expressed in both tissues.

Since the beginning of 2010, it is well established that Dp427 was notably expressed in bipolar cells and proportionally more expressed in cone- than in rod-associated synapses compared with Dp260, while Dp427, Dp260, Dp140, and Dp71 are expressed in inner nuclear layer neurons [3]. Note also that cognitive impairment was also linked to the role of various forms of dystrophin in the central nervous system. Dp427 and Dp71 were thus shown to be involved in synapse organization and function, and distinct Dp71 spliced variants (including those lacking exon 78) were detected in different neuronal subdomains [4]. It was demonstrated with recent approaches that the loss of mammalian brain dystrophins (Dp427, Dp71) impacts on the ultrastructural organization of central glutamatergic synapses, which may explain some of the alterations of synapse function and plasticity that contribute to intellectual disability in DMD [5]. Furthermore, studies on Dp71-null mice eye showed retina lesions with vascular inflammation and degeneration [6].

Retinal function by electroretinography was already studied in the 90's for Becker muscular dystrophy and DMD patients. Most of them had abnormal electroretinograms with reduced amplitude of the b-wave under scotopic conditions [7].

Moreover, in 2007, a study evaluating color vision in 44 DMD patients, 32 of which with deletion downstream of exon 30, showed that 66% among those had a red-green color defect. No color defect was found in the 12 patients with deletion upstream of exon 30 [8].

According to more recent studies in DMD patients and heterozygous DMD carriers, dystrophin is required for the

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proper function of retinal mechanisms underlying ON–OFF, contrast sensitivity, luminance and red-green cone opponent responses [9, 10]. In fact, using the mdx3Cv mice as a DMD model, a full demonstration between the asymmetrical ON versus OFF ERG alterations under mesopic versus photopic vision was recently described. As gene therapy was obtained in dystrophin Dp71 deficient mice with efficient blood-retinal barrier restoration and edema reabsorption [11], this leads us to draw the attention of our colleagues to the important potential clinical analyzes that they might consider in the hope of better management of the quality of life of such a patient.

Taken these data together, we suggest the authors to propose, if not done yet, an examination of visual function including color vision, contrast sensitivity, and electroretinography, along with a retinal optical coherence tomography, to this patient with exon 78 deletion in DMD gene.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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