Letter

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What is the Ocular phenotype associated with a dystrophin deletion of exons 12-29?

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Summary **Duchenne muscular dystrophy (DMD) is a result of a X-linked recessive inherited mutation of the *DMD* gene which contains 79 exons. This rare disease is passed on by the mother who is called a carrier. Primarily it affects boys, but in rare cases it can affect girls. Dystrophin protein is mostly located in skeletal and cardiac muscles, which explains muscular and cardiac manifestations in symptomatic female DMD-carriers. Dystrophin is also present in extramuscular tissues. Some dystrophin isoforms are exclusively or predominantly expressed in the brain or the retina. It has been reported that DMD patients and DMD-carriers present normal visual acuity, but abnormal electroretinographic findings. As symptomatic female DMD are very rare, ophthalmic screening of the female patient with deletions of exons 12-29 is valuable. Studying the functional relationship between ocular symptoms and related different deletions of exons dystrophin gene may further elucidate the pathophysiology in DMD.**

Keywords: Duchenne muscular dystrophy, female carrier, ophthalmology, retina, electroretinogram

We read with interest the case reporting for the first time a female Duchenne muscular dystrophy (DMD)-carrier harboring deletions of exons 12-29, and presenting a muscular/myocardiac phenotype (*1*). It would be instructive to study the ocular phenotype in this patient, for assessing whether these deletions affect the retina.

Indeed, according to existing literature (Table 1), dystrophin isoforms (Dp427, Dp260, Dp140, Dp71) are expressed highly in different retinal layers (*2*). Any disturbance of these protein products is responsible for electroretinogram (ERG) abnormalities. Position of the mutation is the key factor of the ERG phenotype of DMD patients.

According to more recent studies in DMD patients and heterozygous DMD carriers, dystrophin is required for normal function of retinal mechanisms underlying ON-OFF, contrast sensitivity, luminance and red-green cone opponent responses (*3,4*). Retinal phenotype by electroretinography (ERG) was already studied in the 90's, for DMD patients and DMD carriers. Most of them had abnormal ERG with reduced amplitude of the b-wave under scotopic conditions (*5-7*). Abnormal dark-adapted ERGs were reported to be more frequent in DMD patients with more distal mutations (*8*). Moreover, deletion downstream of exon 30 was more frequently associated with red-green color defect among DMD patients (*9*).

Despite the occurrence of a dystrophin deletion upstream of exon 30 in this DMD-carrier (*1*), we suggest our colleagues to propose a screening of visual function including color vision, contrast sensitivity, and ERG, along with a retinal OCT (Optical Coherence Tomography) to the patient. This may enhance our understanding of the pathophysiology in DMD and optimize the comprehensive treatment.

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Table 1. Major research findings from cited references (*2-9*)

Muntoni *et al*. 2003 (*2*)	▪ Patients with Duchenne mauscular dystrophy (DMD) may have normal visual acuity and abnormal electroretinography (ERG): reduction of the b-wave amplitude in the scotopic ERG. ▪ A relation seems to exist between ERG abnormalities and position of deletions of the dystrophin gene (*DMD*).
Barboni *et al*. 2013 (*3*)	ERGs were recorded using mesopic and photopic stimuli in DMD patients (n = 19), heterozygous DMD carriers (n = 7), and healthy controls (n = 19). ▪ DMD patients had normal visual acuity, but a reduced b-wave in ERG and abnormal contrast sensitivities. ▪ Carriers had normal ERG and contrast sensitivities.
Barboni *et al*. 2016 (*4*)	ERGs were recorded in DMD patients (n = 10), and healthy controls (n = 16). ON and OFF cone-driven retinal responses were analyzed. In DMD patients: ▪ ERGs were abnormal ▪ Function of luminance and red-green cone opponent mechanisms were abnormal.
Sigesmund *et al*. 1994 (*5*)	Ophthalmologic examination including ERGs and DNA analysis were performed in DMD patients (n = 21): ▪ Scotopic ERGs were abnormal ▪ Patients with deletions in the central region of the dystrophin gene had the most severe ERG changes.
Girlanda *et al*. 1997 (*6*)	ERG was performed in DMD patients (n=18), and DMD carriers (n = 12): ▪ Reduction of the b-wave amplitude in the scotopic ERG, mainly in DMD patients ▪ Oscillatory potentials were altered, even in carriers, suggesting that dystrophin may be also involved in retinal circulation.
Pascual Pascual *et al*. 1998 (*7*)	The ratio of B-wave amplitude to A-wave amplitude (B/A amplitude ratio of ERG) was evaluated. It was : ▪ Normal (> 2) in all controls (n = 12), ▪ Abnormal (< 2) in 100% of DMD patients (n = 16), ▪ Abnormal (< 2) in 50% of DMD carriers (n = 4).
Pillers *et al*. 1999 (*8*)	▪ ERGs recorded in DMD patients with known deletions (n = 37) were abnormal in 90% (n = 33) and normal in 10% (n = 4) of patients. ▪ Review of literature: 64 DMD patients with known mutations. The most important determinant in the reduction of the b-wave amplitude in dark-adapted ERG is the mutation position: 94% of DMD patients with more distal mutations had abnormal ERG (versus 46% with mutations of the Dp260 transcript start site).
Costa *et al*. 2007 (*9*)	▪ Color vision was evaluated in 44 DMD patients (12 with deletion upstream of exon 30 and 32 with deletion downstream of exon 30), and 70 healthy controls with no ophthalmological complaints. ▪ Red-green color vision impairment in 66% of DMD patients with deletion downstream of exon 30. ▪ DMD patients with deletion upstream of exon 30 had normal color vision ▪ A positive correlation between abnormal scotopic ERGs and neurodevelopmental disturbances, and the most severe findings were in patients with Dp71 disruption.

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