Open access Journal of
Neurology & Neurosurgery
ISSN: 2476-0501

Juniper Publishers
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Opinion
Volume 10 Issue 4 - April 2019
DOI: 10.19080/OAJNN.2019.10.555794

Open Access J Neurol Neurosurg

Diagnosis of Dysferlinopathies

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Submission: March 18, 2019; **Published:** April 22, 2019

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Opinion

Dysferlinopathies are autosomal, recessive allelic muscle disorders produced by mutations in the dysferlin gene (DYSF) [1]. The disease has different phenotypes including limb girdle 2B, Miyoshi myopathy or distal anterior compartment myopathy among others [2]. Dysferlin is located at the membrane of the muscle fiber and its main function is related with membrane repair after damage. However, dysferlin has also been involved in other processes including intracellular signaling or myoblast differentiation. Dysferlin is expressed in other tissues such as monocytes, heart, kidney and placenta where its function is not completely known [3,4].

Diagnosis of patients with dysferlinopathies can be challenging due to the phenotypic variability and the size of the gene. DYSF is one of the biggest human genes. It spans a genomic region of > 150kb and contains 55 exons that encode a 237 kDa protein composed of 2080 amino acids. More than 250 variants have been identified, and there are not hotspots. Therefore, Sanger sequencing is a time consuming and cost-effective method for mutational screening. Moreover, in 15 to 20% of the patients only one mutation is found and in up to 5% of the patients no mutations are detected. In these cases, the analysis of protein expression can be useful either in the muscle biopsy or in other available tissues [5,6].

Immunohistochemistry (IHC) is a useful method to assess a reduction or absence of dysferlin in skeletal muscle. However, IHC analysis can be misleading because dysferlin can be aggregated in the cytoplasm and reduced in the sarcolemma of necrotic or regenerating fibers [7]. Also, patients with missense mutations that allow synthesis of residual protein may show a positive staining by IHC [8]. On the other hand, dysferlin forms a complex with other proteins to perform its function. Mutations in those proteins can disturb the localization of dysferlin, leading to a secondary deficiency [9,10]. For this reason, the diagnosis of dysferlinopathies can not be made based only in dysferlin expression by IHC. Western-Blot (WB) can be useful to confirm the diagnosis [11].

WB analysis of muscle biopsy is a method more reliable since it allows quantification of the protein and therefore discriminates between patients and carriers of one mutation in DYSF [11,12]. The limitations of WB analysis in skeletal muscle are muscle tissue availability and the invasiveness of the surgical procedure to obtain the sample. An alternative to the muscle biopsy is the analysis of dysferlin expression in peripheral blood CD14+ monocytes [13]. Gallardo and collaborators [8], performed a comparative study in 17 dysferlinopathy patients and 21 patients with other neuromuscular disorders and demonstrated that dysferlin expression in monocytes mirrors that in skeletal muscle using WB. However, IHC of dysferlin in skeletal muscle biopsies can be misleading in some cases such as in patients with calpainopathy. Moreover, De Luna et al. [14] also presented the usefulness of peripheral blood monocytes mRNA as a source to study mutations in the DYSF. In yet another study by Luna et al. [15] dysferlin expression in monocytes was quantified in 20 dysferlinopathy patients, 53 carriers and 80 healthy subjects. They showed that dysferlin levels lower than 23% were found in patients with two mutations in the DYSF, while levels between 24.5% and 78.2% were found in healthy individuals and carriers of a single mutation in the DYSF.

In summary, quantification of dysferlin protein in PBM is an easy non-invasive tool that can be useful to diagnose patients with dysferlinopathy, especially in those cases in whom only one mutation is found. At present, next generation sequencing studies may report either a single known pathogenic mutation or new variants of unknown significance. The existence of an easy diagnostic tool such as the blood-based monocyte test can be very useful to support the diagnosis of dysferlinopathy.

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DOI: 10.19080/OAJNN.2019.10.555794

How to cite this article: Fernández-S E, Diaz-M J, Gallardo E, D Luna N . Diagnosis of Dysferlinopathies. Open Access J Neurol Neurosurg. 2019; 10(4): 555794. DOI: 10.19080/OAJNN.2019.10.555794.