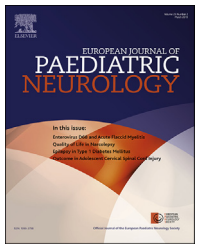
Official Journal of the European Paediatric Neurology Society



Editorial

Nesprinopathy: A multi-faceted genetic disorder

'Nuclear envelopathies' are a group of diseases resulting from mutations of the genes encoding parts of the inner nuclear membrane (Emerin), nuclear lamina (Lamins A and C) and outer nuclear membrane (Nesprins). All have disease causing properties in humans, nesprins being the third in chronology.

Nesprin-1 and nesprin-2 are the largest spectrin repeat proteins which are encoded by two genes, *SYNE1* and *SYNE2*, respectively. Multiple nesprin protein isoforms are generated through alternative transcription. These tissue specific isoforms localise to multiple subcellular compartments, providing additional functions for nesprins other than nucleaer envelope linkage and consequently leading to variable neurological disease phenotypes. There are in total of four different nesprins.[1] Three of these nesprins are known to cause human disease so far.

SYNE1 mutations are known to cause various disease phenotypes including autosomal recessive cerebellar ataxia type 1 (*ARCA1*, or spinocerebellar ataxia type 8-SCAR8) with or without extracerebellar neurological involvement,[2] Emery-Dreifuss muscular dystrophy type 4,[3] and arthrogryposis multiplex congenita.[4]

There is data at hand that *SYNE1* genotype–phenotype correlation may exist. Mutations in the C-terminal regions (KASH domain) of the *SYNE1* and *SYNE2* genes have been identified in patients with muscular disorders. In contrast, mutations in the N-terminus (CHD), are associated with ataxia, after disturbing vesicular transport.[5] It is probably early to derive a conclusion for *SYNE4*, So far, no disease has been identified associated with *SYNE3*.

In this issue, Heike Koelbel and colleagues describe 5 patients from 3 families, in whom multi-gene panel genetic analysis revealed various *SYNE1* mutations which are novel or variant of unknown significance.[6] In the light of the previous literature, they proved the pathogenicity of these mutations by reviewing history, neurological examination, available nerve and muscle biopsies and neuroimaging findings. They denote to three different clinical phenotypes:

1. A myopathic type with mainly distal involvement resembling to Emery-Dreifuss muscular dstrophy and with cardiomyopathy
2. A complicated form of ataxia with mental retardation and peripheral neuropathy being mainly axonal
3. An arthrogrypotic form

All three forms share thumb abnormalities and ultrastructural alterations of nuclear envelope as a requisite. These alterations are also shown in Schwann cell nuclei which predicted possible glial and neuronal involvement. The well described clinical features in this paper along with supporting histology and ultrastructure may be considered at the differential diagnosis stage during evaluation of similar cases. Nesprinopathies are new disorders, the first case (ataxia) was identified in 2007. So, data is only accumulating. Any new case to be diagnosed in any setting may emerge or present with one or more of the stigmata described in this paper, i.e. ataxia and mental retardation, myopathy, neuropathy or even severe dilated cardiomyopathy.

REFERENCES

1. Rajgor D, Shanahan CM. Nesprins: from the nuclear envelope and beyond. *Expert Rev Mol Med* 2013;**15**:e5.
2. Synofzik M, et al. SYNE1 ataxia is a common recessive ataxia with major non-cerebellar features:a large multi-centre study. *Brain* 2016;**193**:1378–93.
3. Zhang Q, et al. Nesprin-1 and -2 are involved in the pathogenesis of Emery Dreifuss muscular dystrophy and are critical for nuclear envelope integrity. *Hum Mol Genet* 2007;**16**(23):2816–33.
4. Attali R, et al. Mutation of SYNE-1, encoding an essential component of the nuclear lamina, is responsible for autosomal recessive arthrogryposis. *Hum Mol Genet* 2009;**18**(18):3462–9.
5. Zhou C, et al. Novel nesprin-1 mutations associated with dilated cardiomyopathy cause nuclear envelope disruption and defects in myogenesis. *Hum Mol Genet* 2017;**26**(12):2258–76.
6. Kolbel H, et al. Characteristic clinical and ultrastructural findings in nesprinopathies. *Eur J Paediatr Neurol* 2019;**23**(2):254–61.

Hatice Bektaş
Department of Paediatric Neurology, Hacettepe Children's Hospital, Ankara, 06100, Turkey

Haluk Topaloglu*
Department of Paediatric Neurology, Hacettepe Children's Hospital, Ankara, 06100, Turkey

*Corresponding author.
E-mail address: htopalog@hacettepe.edu.tr

https://doi.org/10.1016/j.ejpn.2019.02.011