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Letter to the Editor

LHON in Siberia

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With interest we read the article by Starikovskaya *et al.*, about 85 patients with Leber's hereditary optic neuropathy (LHON) and 83 healthy carriers from West Siberia (Starikovskaya, E. *et al.*, 2019). Pathogenicity of the variants was assessed by application of PolyPhen-2, MutPred1.2, MutPred-2, PROVEAN, and SIFT (Starikovskaya, E. *et al.*, 2019), The authors concluded that the mutational spectrum of LHON patients from Western Siberia varies considerably from that of European LHON cohorts (Starikovskaya, E. *et al.*, 2019). The study has a number of shortcomings.

The main shortcoming of the study is that variants, from which it is not known if they are definitively pathogenic, were not sufficiently tested for their potential pathogenicity. In-silico methods, such as PolyPhen, MutPred1.2, PROVEAN, and SIFT, may be misleading regarding the pathogenic relevance, why more profound methods such as ultrastructural investigations, biochemical investigations, immune-histochemistry, measurement of oxygen consumption, ATP, and reactive oxygen species (ROS) production, or cybrid studies should be applied. It is also crucial that segregation of the phenotype with the mutation is documented within a family (Finsterer, J. *et al.*, 2018). The pathogenicity can be assessed by application of a modification of the Yarham score (Finsterer, J. *et al.*, 2018). Thus, causality of unreported variants, such as m.4766A>G, 13105A>G, 14002A>G, 4659G>A, 14484T>C and the rarely reported variants m.10663T>C and m.3646G>A (Al-Kharashi, M. *et al.*, 2016) remains unproven.

A further shortcoming is that heteroplasmy rates of the variants detected were not provided. Knowing heteroplasmy rates is crucial for assessing the outcome of a phenotype and for genetic counselling (Chinnery, P.F., 2000). Since heteroplasmy rates can vary considerably between tissues, it is worthwhile to know heteroplasmy rates not only from a single affected tissue but from several affected tissues.

LHON may not only manifest in the retinal ganglion cells and the optic nerve (pure LHON) but also in organs/tissues other than the retina and the optic nerve (LHON-plus) (Finsterer, J., & Zarrouk-Mahjoub, S. 2016). These other organs include the brain (epilepsy, dystonia, migraine, mental retardation, transverse myelitis, white matter lesions, olivo-cerebellar degeneration, gaze palsy, nystagmus, cerebellar ataxia, dysarthria), the heart (noncompaction), endocrine organs, arteries, peripheral nerves, and the bone marrow (Finsterer, J., & Zarrouk-Mahjoub, S. 2016). Since multisystem involvement may not always be clinically evident, it is necessary to prospectively investigate LHON patients for subclinical involvement of other organs. Thus, we should know if

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the 85 manifesting patients and the 83 asymptomatic mutation carriers were prospectively investigated for LHON-plus. Particularly we should be informed which other organs were affected and if other features were more or less predominant that the visual problem. Knowing multisystem involvement is crucial for assessing the prognosis and outcome of an individual patient.

Another shortcoming is that long-term data about the included patients were not provided. Knowing the long-term course of LHON is not only useful for broadening the phenotypic description but also to know which patient had a benign course or recovered spontaneously (Moon, Y. *et al.*, 2019). Particularly from the variants m.14484 and 11778 it is well appreciated that they may resolve spontaneously (Stone, E. M. *et al.*, 1992).

On the one hand the authors mention that their patients do not know their family history (Starikovskaya, E. *et al.*, 2019), and on the other hand the rate of sporadic cases is reported as 40% (Starikovskaya, E. *et al.*, 2019). We should know if the high rate of sporadic cases is due to insufficiently taken family histories. In table 1 it remains unclear why the authors talk about the "estimated number of affected / unaffected patients". Is this wording due to uncertainty about the family histories?

In summary this impressive study has a number of shortcomings, which need to be addressed before drawing final conclusions. Multisystem involvement should be addressed, heteroplasmy rates should be provided, and the pathogenicity of novel variants should be confirmed by more sophisticated methods than in-silico testing.

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