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Peculiarities of the m.3243A > G variant in *MT-TL1* leave medicine unprecise

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With interest we read the review by Boggan et al. about the genetic, pathogenetic, clinical, diagnostic, and therapeutic peculiarities of the m.3243A > G variant in *MT-TL1* [1]. We have the following comments and concerns.

Factors influencing the phenotype of the m.3243A > G variant in addition to tissue/organ segregation, heteroplasmy, bottleneck, mtDNA copy number, nDNA determinants, environment, and age, as outlined in Fig. 1, are sex [2], haplotype [3], and mtDNA polymorphisms [4].

The m.3243A > G variant may not only be associated with clinical manifestations, as shown in Fig. 1, but also with a number of other features, as listed in Table 1. The phenotypic spectrum of the variant is thus more variegated than usually anticipated. Not only the brain, eyes, ears, endocrinium, heart, guts, muscles, and kidneys may be affected but also the vestibulum, peripheral nerves, bones, bone marrow, skin, and the arteries (Table 1) [5]. There are even indications that the cellular immune system can be impaired in m.3243A > G carriers.

Stroke-like lesions (SLLs), the morphological correlate of a stroke-like episode (SLE), may not only be distinguished in the acute stage from ischemic stroke by the non-vascular extension of the lesion, but also by progression of the lesion, by hyperperfusion, by reduced oxygen extraction, and by a vasogenic edema. SLEs not necessarily are associated with seizures or epileptiform discharges on electroencephalography.

We agree that double-blind placebo-controlled trials for treatments of SLEs are lacking, but it has to be stressed that some patients with SLEs benefit from anti-seizure drugs, NO-precursors, antioxidants, steroids, or even the ketogenic diet. Whether the application of anti-seizure drugs in the absence of seizures or epileptiform discharges is justufied during a SLE, remains speculative, but as long as the epileptogenic hypothesis explaining the pathogenesis of SLEs is unproven, aggressive anti-epileptic treatment does not seem to be justified in this indication.

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Table 1
Phenotypic manifestations of the m.3243A > G variant.

Organ/tissue	Abnormality	Reference
Brain	Stroke-like episode	[Pronicki 2002]
	Epilepsy	[Pronicki 2002]
	Migraine-like headache	[Tsujikawa 2014]
	Cerebellar atrophy	[Fromont 2009]
	White matter lesions	[Fromont 2009]
	Cortical, white matter atrophy	[Yokoyama 2010]
	Hypopituitarism	[Pronicki 2002]
	Intracranial calcifications	[Pronicki 2002]
	Cognitive impairment	[Fromont 2009]
Eyes	Pigmentary retinal degeneration	[Pronicki 2002]
	Corneal polymegathism	[Bakhoum 2018]
	Choriocapillaris atrophy	[Tsang 2018]
Ears	Hypoacusis	[Pronicki 2002]
Vestibulum	Imballance, gait distrubance	[Hougaard 2019, Inoue 2019]
Endocrinium	Diabetes	[Tsang 2018]
Heart	Hypertrophic cardiomyopathy	[Finsterer 2018]
	Dilated cardiomyopathy	[Finsterer 2018]
	Noncompaction	[Finsterer 2018]
	Arrhythmias/conduction defects	[Finsterer 2018]
Gut	Vomiting	[Pronicki 2002]
	Abdominal pain	[Pronicki 2002]
	Sialoadenitis	[Pronicki 2002]
	Pancreatitis	[Ishiyama 2013]
Liver	Liver failure	[Takahahsi 2008]
Kidney	Renal insufficiency	[Alcubilla-Prats 2017]
	Focal segmental glomerulosclerosis	[Alcubilla-Prats 2017]
	Hyponatremia	[Hall 2015]
	Hypophosphatemia	[Hall 2015]
	Hypomagnesemia	[Hall 2015]
Muscle	Myopathy	[Zhou 2018]
	Lactic acidosis	[Fromont 2009]
Nerves	Polyneuropathy	[Zhou 2018]
	Small fibre neuropathy	[Luigetti 2018]
Arteries	Carotid artery dissection	[Mancuso 2016]
Bone marrow	Anemia	[Tinsa 2009]
	Leukopenia	[Tinsa 2009]
Bone	Deformities	[Pronicki 2002]
Skin	Atopic dermatitis	[Pronicki 2002]
	Local melanoderma	[Pronicki 2002]
	Asymmetric vascular dilatation	[Pronicki 2002]

Author contribution

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Declaration of Competing Interest

There are no conflicts of interest.

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