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Letter to the Editor

Before attributing CPEO and ptosis to the variant m.14819T > G its pathogenicity needs to be established

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With interest we read the article by Nomura et al. about a 47yo female with ptosis and chronic progressive external ophthalmoplegia (CPEO) being attributed to a single mtDNA deletion, the mtDNA variant m.14819T > G, or the heterozygous *POLG1* variant c.2890C > T [1]. The latter variant was also found in her brother who only manifested with CPEO without ptosis but not in the mother who manifested with ptosis and CPEO [1]. The mtDNA variant m.14819T > G was also found in the brother and the mother [1]. We have the following comments and concerns.

A shortcoming of the study is that heteroplasmy rates of the variant m.14819T > G and the single mtDNA deletion were not provided. Determination of heteroplasmy rates in various tissues such as hair follicles, buccal mucosa cells, skin fibroblasts, muscles cells, or urinary epithelial cells is crucial, as they can strongly determine the phenotype and may explain the variable disease expression and onset of clinical manifestations in the three probands.

A further shortcoming is that mother and brother were not tested for the single mtDNA deletion. Since single mtDNA deletions typically manifest with ptosis and CPEO [2] and may be inherited in 4% of the cases [3], it is crucial that both brother and mother were also investigated for this variant.

Another shortcoming is that the pathogenicity of the m.14819T > G variant was not assessed by application of the modified Yarham score, which validates the items number of publications, heteroplasmy, disease segregation with the variant, biochemical respiratory chain defect, variant segregation with biochemical defect in single fiber studies, evidence of pathogenicity on cybrid studies, evolutionary conservation of variant, and histopathological findings [4].

Arguments against the pathogenicity of the *POLG1* variant c.2890C > T are that it occurred only in the heterozygous form and that the mother did not carry this variant. Unfortunately, the father was not tested for the *POLG1* or mtDNA variants found in his children. All p.R964C variants so far reported occurred either in the homozygous or compound heterozygous form (Table 1) [5,6,7,8,9]. This particular variant was made responsible for non-syndromic ovarian dysfunction in a Chinese female from consanguineous parents who was homozygous for the c.2890C > T variant [5]. A patient with ataxia neuropathy spectrum (ANS) disorder carried the c.2890C > T variant in a compound heterozygous form together with the p.A862T variant [6]. In another patient, homozygous for the variant c.2890C > T and HIV-positive, the mutation manifested with lactic acidosis exclusively [7]. Activity of POLG1 was reduced to 14% of normal [7]. In a study of 136 individuals carrying informative *POLG1* variants, one carried the compound heterozygous variants c.2890C > T and c.2884G > A (Table 1) [8]. This proband manifested phenotypically with ataxia, muscle weakness, and central hypoventilation. In two siblings with multisystem mitochondrial disorder (MID) the phenotype was attributable to the compound heterozygous *POLG1* variants c.2890C > T and c.2284G > A [9].

Missing in the report is if mother and father of the index case were consanguineous or not. This information is crucial as the Chinese female carrying the *POLG1* mutation originated from consanguineous parents [5].

Table 1
Patients carrying the *POLG1* variant p.964R > C.

Age	Sex	Phenotype	Dosage	Reference
47	f	CPEO, ptosis	heterozygous	[1]
np	m	CPEO	heterozygous	[1]
17	m	ANS	compound heterozygous	[6]
34	f	Lactic acidosis	homozygous	[7]
14	np	Ataxia, weakness, central hypoventilation	compound heterozygous	[8]
27	m	Ataxia, focal myoclonic epilepsy, RLS Neuropathy,	compound heterozygous	[9]
23	f	Epilepsy, delayed psychomot. Development quadruparesis, cerebellar syndrome	compound heterozygous	[9]

np: not provided, CPEO: chronic progressive external ophthalmoplegia, ANS: ataxia neuropathy spectrum disorder (ataxia, exercise intolerance, cerebellar ataxia), RLS: restless leg syndrome.

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Overall, this interesting study could be more meaningful if the several shortcomings were addressed. Before declaring a certain variant as causative, it should be confirmed in all three probands and its pathogenicity needs to be established.

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Josef Finsterer
Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria
E-mail address: fifigs1@yahoo.de.