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Letter to the Editor

Is *GMPR* Truly The 19th Gene Associated With Pure Progressive External Ophthalmoplegia?

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In a recent article, Sommerville *et al*., reported about a 73yo female with late-onset mitochondrial myopathy manifesting in the extra-ocular, facial, and limb muscles (Sommerville, E.W. *et al.,* 2019). The phenotype was attributed to the novel, heterozygous variant c.547G>C in *GMPR*.(2019) We have the following comments and concerns.

We do not agree with the classification of the index patient as progressive external ophthalmoplegia (PEO) (Sommerville, E.W.,*et al*.,2019). The patient additionally had weakness of the facial muscles and proximal limb muscles. Respiratory function was not assessed. There was no systematic investigation for multisystem disease. Since GMPR is highly expressed in the muscle, myocardium, and kidney, (Deng Y, *et al*.,2002) cardiac and renal involvement can be also expected. Generally, mitochondrial disorders (MIDs) frequently manifest progressively in several different organs/tissues such as the brain, eyes, ears, endocrine organs, heart, lungs, gastrointestinal tract, kidneys, none marrow, cellular immune system, cartilage, and skin.(Nesti, C., *et al*.,2019) Of particular importance are investigations of the heart, since cardiac disease may strongly determine the outcome of MID patients.

Since mutations in *GMPR* are associated with an increased risk of atherosclerosis, particularly coronary heart disease, (Waterworth, D.M.,*et al*.,2010) it should be reported if the individual history of the index-patient was positive for myocardial infarction or anginal chest pain, and if ever a stress-test, coronary angiography, or perfusion scintigraphy had been carried out.

Missing in this report is the family history and genetic work-up of relatives. We should know if any of the index patient's first degree family members had myopathy or carried the culprit variant.

To better understand the function of GMPR it could be worthwhile to apply high-resolution 31P-file-cycling relaxometry. (Rosenberg, M.M.,*et al*.,2016).

Overall, this thorough study may profit from re-classification of the condition as PEO-plus, a prospective investigation of tissues other than the skeletal muscle, from evaluation for atherosclerosis, and from provision of a detailed family history and genetic investigations of the patient's first degree relatives.

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