

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, bone 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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