

## LETTER TO THE EDITOR

### How would a completely homogeneous malignant hyperthermia susceptible sample be?



Dear Editor,

We read with interest the letter to the editor by Finsterer et al.<sup>1</sup> We appreciated the interest in our article<sup>2</sup> and the comments, which gave us the opportunity to include additional data from our research and deepen the discussion on how would a completely homogeneous malignant hyperthermia (MH) susceptible sample be.

First, specifically regarding the additional data of our sample, all patients selected for MH investigation in our service are initially submitted to clinical investigation, with detailed standardized general clinical history and specific questionnaire for anesthetic MH.<sup>3</sup> A complete general physical and neurological examination is then performed. Next, an extensive laboratory evaluation is ordered, with an electrocardiogram, chest X-Ray, complete blood count, and serum biochemistry including electrolytes, kidney and liver function, and research for endocrine diseases. This evaluation allowed, as already stated in our article,<sup>2</sup> to “exclude patients with other chronic morbidities and/or neurological disorders, or those under chronic use of medications”. The MH non-susceptible (MHN) patients underwent the In Vitro Contracture Test (IVCT) because they were relatives of malignant hyperthermia susceptible (MHS) patients. Regarding group sizes, the sample size calculation has been already detailed in the article.

All patients filled out the forms in person, by themselves, in the presence of the researchers. The scales (fatigue severity scale, Baecke habitual physical exercise scale) and the Beck depression inventory are based on self-assessment and widely employed for clinical studies in many diseases, such as the neuromuscular disorders.<sup>4</sup> The clinical studies of our group are preliminary and are being followed by additional available studies with objective methods such as cycle ergometry, where the physical activity and environmental conditions can be fully controlled. The great advantage of scales over the objective methods is their accessibility and low cost for fast detection by the health professional in the clinical setting.

The molecular study already disclosed ryanodine receptor type 1 (*RYR1*) gene variants related to 18 of the 22 MHS individuals included in our article;<sup>2</sup> four are still under study. The contracture test is still a gold standard for MH, due to the genetic heterogeneity of MH.<sup>5</sup> The finding of a variant in genes related to MH, such as the *RYR1* gene, is usually not diagnostic until its validation is performed by means of strict criteria that consider associated data on positive contracture tests and calcium release studies, showing channel gain-of-function (i.e., increased calcium release).<sup>5-7</sup> Moreover, there are hundreds of variants reported in the principal gene related to MH, the *RYR1* (<https://databases.lovd.nl/shared/genes/RYR1>). That is the reason why only 66 *RYR1* gene variants are accepted as pathogenic by the European Malignant Hyperthermia Group (<https://www.emhg.org/diagnostic-mutations>) and there is a variant curation expert panel specifically working on MH variants.<sup>7</sup> Due to the rarity of the MH crisis and to the genetic variability of MH, with a candidate gene still absent in many families, a significant and completely homogeneous MHS sample with the same causal variant in the same gene would be a challenging task. Alternatively, in the current state of knowledge, a significant sample with the commonest characteristic of channel gain-of-function would be more feasible.

With the exception of metabolic diseases such as glycogen and lipid storage diseases,<sup>8</sup> there are no extensive clinical studies dealing with the possible effects of diet on clinical complaints like fatigue in neuromuscular disorders in general and MH in particular. This possibility could be a theme of future research in the field. About the relationship between fatigue and exercise intolerance, our article<sup>2</sup> does not imply that fatigue and effort intolerance are equal, but rather that, when fatigue and effort intolerance are found in the same patient, they can arrive from the same disease, thus being, as suggested by Grassi et al., 2015, “two sides of the same coin”.<sup>9</sup>

Finally, we would like to comment on why MH susceptibility is generally considered an autosomal dominant disorder<sup>5-7</sup> and core myopathy autosomal dominant or recessive,<sup>10</sup> despite both being associated with *RYR1* gene variants in many families. Patients with core myopathy can harbor one variant in the *RYR1* gene (heterozygous), two identical variants in the *RYR1* gene (homozygous), or two different variants in the *RYR1* gene (compound heterozygous).<sup>11</sup> If any of

these variants are associated with gain-of-function and increased calcium release, their relatives with even only one of these variants, despite not presenting core myopathy, are at risk of MH crisis if exposed to halogenated anesthetics and/or succinylcholine. The STAC3 gene was associated with a recessive clinical myopathy and episodes of MH, but results of IVCT in heterozygous relatives with the described variants remain to be published.

## Conflicts of interest

The authors declare no conflicts of interest.

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