LETTER TO THE EDITOR

Reply: Is SIGMAR1 a confirmed FTD/MND gene?

Nathalie Bernard-Marissal,1 Jean-Jacques Médard,2 Hamid Azzedine3 and Roman Chrast4

1 Neurodegenerative Studies Laboratory, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland
2 Department of Medical Genetics, University of Lausanne, CH-1005 Lausanne, Switzerland
3 Institute of Neuropathology, Uniklinik RWTH Aachen University, 52074 Aachen, Germany
4 Department of Neuroscience and Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden

Correspondence to: Roman Chrast,
Department of Neuroscience and Department of Clinical Neuroscience,
Karolinska Institutet,
171 77 Stockholm,
Sweden
E-mail: Roman.Chrast@ki.se

Correspondence may also be addressed to: Nathalie Bernard-Marissal,
E-mail: nathalie.bernard@epfl.ch
Hamid Azzedine,
E-mail: azzedine.hamid@yahoo.fr, hazzeddine@ukaachen.de

Sir,

We thank Drs Pickering-Brown and Hardy for their comment and interest in our recent article regarding the role of SIGMAR1 in motor neuron biology. In our study, we used a combination of in vivo and in vitro models of loss-of-function of SIGMAR1 to provide new insight into the role of endoplasmic reticulum-mitochondria contacts, calcium homeostasis and mitochondrial function for maintenance of motor neuron integrity (Bernard-Marissal et al., 2015). Regarding the comment from Pickering-Brown and Hardy, it is important to reiterate that our interest in the role of SIGMAR1 in motor neurons was based on multiple previous studies showing that (i) the Sigmarr1 knock-out mouse presents motor disabilities (Langa et al., 2003; Mavlyutov et al., 2010); (ii) SIGMAR1 is highly expressed in motor neurons (Mavlyutov et al., 2010); (iii) stimulation of SIGMAR1 function via its agonists Pre-084 is neuroprotective in a model of motor neuron disease (Mancuso et al., 2012); (iv) that SIGMAR1 is dysregulated in tissues from patients with amyotrophic lateral sclerosis (ALS) (that did not show C9orf72 expansion) (Prause et al., 2013); and (v) that mutations in SIGMAR1 are implicated in frontotemporal lobar degeneration co-occurring with ALS (FTLD-ALS) (Luty et al., 2010) and in juvenile ALS (Al-Saif et al., 2011); as representative reports.

Some of the genetic data, which are the core of the comment from Pickering-Brown and Hardy, were recently re-evaluated based on the discovery that affected individuals from the family originally reported by Luty and colleagues carry, in addition to the 3' UTR SIGMAR1 variant, also the C9orf72 repeat expansion (Dobson-Stone et al., 2013). The unrelated case with SIGMAR1 variant also reported by Luty and colleagues, however, does not carry the C9orf72 repeat expansion (Dobson-Stone et al., 2013). Also, oligogenic aetiology was previously suggested in some ALS cases carrying the C9orf72 repeat expansion (Lattante et al., 2015).

We anticipate that further genetic studies will help to provide additional insight into the contribution of SIGMAR1 to motor neuron disease. In the meantime, the characterization of the role of SIGMAR1 in motor neurons is already helping us to unravel their biology and pathophysiology.
References


