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LETTER TO THE EDITOR

Reply: Is *SIGMAR1* a confirmed FTD/MND gene?

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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 *Sigmar1* 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.

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