LETTER TO THE EDITOR

Is SIGMAR1 a confirmed FTD/MND gene?

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Dear Sir,

Frontotemporal dementia (FTD) and the related condition motor neuron disease (MND) can have a genetic component to their aetiology. The genes reported causing these diseases have been identified using classical genetic linkage but more recently the use of genome-wide association studies, exome sequencing and next generation DNA sequencing technologies have accelerated the pace at which genes are identified and reported. We read with great interest the recent publication in Brain of Bernard-Marissal et al. (2015) describing a motor neuron degeneration phenotype, but without any reporting of a TDP-43 (TARDBP) pathology, in mice lacking the SIGMAR1 gene. It was reported in 2010 that a family with frontotemporal dementia and motor neuron disease (FTD + MND) with genome-wide significant linkage to chromosome 9p had a mutation in the 3’ UTR if the SIGMAR1 gene (Luty et al., 2010). A subsequent paper reported a missense mutation in a family with a juvenile motor neuron disease phenotype (Al-Saif et al., 2011). However, it was later reported that the original family with a 3’ UTR variant also has a repeat expansion mutation in C9orf72 (Dobson-Stone et al., 2013). Furthermore, other single cases with reported SIGMAR1 variants have also been shown to harbour C9orf72 expansions (Belzil et al., 2013). In light of this, it is likely that the disease in the original family reported by Luty et al. is caused by the C9orf72 expansion rather than the 3’UTR variant in SIGMAR1. If this is the case then there are no reported pedigrees with a FTD + MND phenotype, linkage to chromosome 9p with a LOD score reaching genome-wide significance, and a mutation in SIGMAR1. This scenario, therefore, questions the validity of SIGMAR1 being a FTD + MND causative gene. It is, of course, of real interest that SIGMAR1 knockout mice have a motor neuron degeneration phenotype to those working in the field of motor neuron disease; however, this in itself does not provide extra support of this gene being causative for MND or FTD. Given the increasing rate, from improvements in next generation DNA sequencing technologies, of variants claimed to be disease-causing it is important to verify and validate such genetic assertions before lengthy, time consuming and expensive functional and modelling follow-up studies are performed.

References