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LETTER TO THE EDITOR

Reply: Adult-onset distal spinal muscular atrophy: a new phenotype associated with *KIF5A* mutations

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Sir,

In 2018, we provided evidence that splice site mutations in the C-terminal cargo binding domain of *KIF5A* are a cause of familial amyotrophic lateral sclerosis (FALS) (Brenner *et al.*, 2018). Shortly thereafter, a genome-wide significant enrichment of *KIF5A* loss-of-function mutations in FALS patients was confirmed by a large whole exome sequencing study comprising 1138 index FALS cases and 19 494 controls (Nicolas *et al.*, 2018). In both studies, pathogenic mutations clustered predominantly in the C-terminal cargo binding domain of *KIF5A* and are predicted to affect splicing of exon 27. The disease course of FALS patients carrying C-terminal *KIF5A* mutations is rather heterogeneous. While in our cohort the median survival of *KIF5A* loss-of-function mutation carriers was 40.5 months ($n = 8$), Nicolas *et al.* reported a median survival of 117 months ($n = 17$). Remarkably, three patients with C-terminal *KIF5A* mutation in the latter cohort survived more than 18 years. By comparison, the median survival time of ALS patients is ~20–36 months in countries with European ancestry (Chiò *et al.*, 2009) or 31 months in southern Germany (Rosenbohm *et al.*, 2017). FALS patients carrying C-terminal *KIF5A* loss-of-function mutations showed asymmetric affection of upper and lower motor neurons consistent with a classical ALS phenotype.

We read with interest the Letter to the Editor from de Fuenmayor-Fernández de la Hoz *et al.* (2019) postulating an adult-onset distal spinal muscular atrophy as a new phenotype associated with a novel *KIF5A* missense mutation. The authors describe a family with five patients (four siblings and their father) who developed slowly progressive symmetric myatrophic palsy of the upper and lower extremities, with predominant involvement of distal extensor muscles while not displaying upper motor neuron signs. The authors did not mention whether the deceased father showed upper motor neuron signs nor did they report the cause of his death. Apart from the father, who showed a survival after disease onset of 20 years, all affected second generation family members are still alive, with a maximal survival after disease onset of 11 years to date.

Electroneurography showed no signs of motor or sensory neuropathy and electromyography is consistent with muscular denervation. Histology of a muscle biopsy showed rimmed vacuoles and some inflammatory infiltration. This finding can be unspecific and a consequence of a primary neurogenic degeneration (Jokela *et al.*, 2016). However, in the muscle biopsies presented here, the vacuoles are quite large, abundant and not combined with muscle fibre atrophy (in Patient II-3). It is thus tempting to speculate about a primary vacuolar myopathic component. Although current data suggest that *KIF5A* expression is neuron-specific, it might nevertheless be expressed at variable levels in subsets of muscles, or expression could be increased in denervated muscle fibres.

Altogether, the authors assume a progressive muscular atrophy (PMA) in this family. Using whole exome sequencing they found the missense variant c.G802A/p.A268T located in the N-terminal domain of the KIF5A protein in two affected family members. Sanger sequencing of the other family members revealed co-segregation of the variant with the observed phenotype in four affected family members. The authors conclude that the *KIF5A* variant is the most likely cause of the observed phenotype in this pedigree.

The reported syndrome would indeed be consistent with the diagnosis of PMA in this family. However, as the disease started with and is characterized by predominant palsy of distal extensor muscles in all affected family members, lower motor neuron dominant ALS with a later development into a classical ALS phenotype or upper motor neuron signs masked by lower motor neuron involvement cannot be ruled out at this point. Additional studies to assess a possible upper motor neuron lesion have not been performed by the authors, e.g. transcranial motor evoked potential or MRI/diffusion tensor imaging of the corticospinal tracts. The slow progression *per se* does not argue against ALS as a significant number of ALS patients survive longer than 10 years untreated, including a patient with *KIF5A* mutation who survived more than 264 months (Nicolas *et al.*, 2018).

The variant described is located in the N-terminal domain, whereas proven pathogenic variants in ALS are restricted to a mutational hotspot in the C-terminal domain (Brenner *et al.*, 2018; Nicolas *et al.*, 2018). Because the most distal muscles (e.g. extensor hallucis or toe flexors and extensor) are only mildly affected, the clinical picture as well as the electrophysiological findings are indeed not in agreement with a hereditary neuropathy that is frequently observed with point mutations in the N-terminal part of the KIF5A protein.

From a genetic point of view, a caveat is necessary, although co-segregation of the reported novel *KIF5A* variant and the phenotype appears suggestive. However, based on this small pedigree, the probability of a chance finding is ~6.25%, taking into account four meioses and siblings with known genotype and phenotype, respectively, in addition to the index patient. Moreover, an unaffected sibling who was tested negative for the variant could still develop the PMA syndrome, which would strongly argue against causality in the absence of the variant. Overall, it cannot be excluded that a different genetic variant is responsible for causing the observed phenotype in this family. It would furthermore be interesting to know the other rare variants

that must have been detected by the next generation sequencing performed.

In conclusion, the evidence presented largely supports a PMA phenotype in this family, which could be caused by the newly reported *KIF5A* variant c.G802A/p.A268T, while further clinical and genetic studies are required to finally prove the possible causation of PMA by N-terminal *KIF5A* mutations.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

For full details see Supplementary material.

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