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Letter to the Editor

Novel TBK1 LoF variant in a family with upper motor neuron predominant motor neuron disease

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Dear Editor,

Amyotrophic lateral sclerosis (ALS) is usually sporadic, but 20% of European ancestry cases have a family history of ALS or frontotemporal dementia (FTD) [1]. More than 30 genes confer a higher risk for ALS, and *C9orf72*, *TARDBP*, *SOD1* and *FUS* account for nearly 70% of all familial (fALS) cases [1]. Tank-binding kinase 1 (*TBK1*) is an established causal gene associated with 1% of fALS and/or FTD [2]. It codes for a multifunctional kinase involved in multiple cellular processes, such as neuroinflammation and autophagy [3]. Both loss-of-function (LoF) and missense mutations are associated with an increased risk for ALS-FTD spectrum and mutations that cause a 50% reduction of TBK1 protein levels are considered pathogenic [4,5].

The clinical phenotypes associated with *TBK1* mutations are heterogeneous. In an Italian cohort age of disease onset ranged from 36 to 81 years, the onset was spinal in all 7 cases, and phenotype ranged from Charcot-type ALS to flail-arm and pure lower motor neuron (LMN) disease, with very variable progression rates. Cognitive impairment was identified in 3 patients [7]. In a German cohort the onset was spinal with predominant LMN signs in the 4 patients included, without cognitive impairment [8]. Incomplete, but high, penetrance has been described in TBK1 LoF carriers [6]. A Belgian comparative study described 7 ALS and 1 ALS-FTD patient with *TBK1* mutations, with late onset ALS (mean age of 58.1 years at first symptoms) and incomplete penetrance, mostly with bulbar-onset and prominent upper motor neuron (UMN) signs and one patient with extrapyramidal features [9]. In fact, progressive supranuclear palsy-like and cerebellar syndromes have recently also been associated with TBK1 mutations [10].

We observed two sisters with quite heterogeneous presentation. Patient 1– A 60 years-old female presented with progressive dysarthria and dysphagia for 6 months, rapidly progressing to upper and lower limb weakness. No relevant family history was disclosed. On examination we observed tongue fasciculations associated with poor tongue movements in spite of absent atrophy, spastic tetraparesis with generalized very brisk tendon reflexes, pathological jaw jerk and bilateral Babinski sign, and diffuse limb fasciculations. Brain MRI was unremarkable. The EMG showed diffuse loss of motor units involving the bulbar region, nerve conduction studies were normal. ALS diagnosis was made according to the Awaji criteria [11]. On follow-up, ALSFRS-R declined at a rate of 0.92/month, evolving to aphagia and respiratory insufficiency. She underwent gastrostomy and non-invasive ventilation, dying 4 years after diagnosis without clinical signs of FTD. Patient 2 – A 64 years-old woman, sister of patient 1, presented with progressive severe left spastic hemiparesis for 10 months, without bulbar symptoms. On observation she had generalized limb hyperreflexia and bilateral Babinski sign, without bulbar signs, limb wasting or fasciculations. Brain and spinal cord MRI were unremarkable. EMG did not disclose loss of motor units and nerve conduction studies were normal. She was diagnosed with UMN disease, Mills phenotype. She has been followed for 3 years, progressing to severe spastic tetraparesis, without LMN signs. ALSFRS-R decayed by 0.81/month but bulbar involvement was absent. Regularly repeated neurophysiological investigations (6-months interval) have confirmed no signs of motor units loss.

Patient 2 was negative for *C9orf72* and was then analyzed with a panel including 26 ALS relevant genes. The only mutation detected was a heterozygous base pair deletion in exon 19 of *TBK1* (NM_013254.3): c.2044del, p. Thr682Hisfs*2. This LoF mutation is novel and quantification of TBK1 protein expression was not done. However this mutation is likely pathogenic due to haploinsufficiency, since mutations of this type were described to create a termination codon leading to an almost complete loss of expression of 1 *TBK1* allele [6]. Moreover, simulation of this mutation on MutPred-LOF (http://mutpredlof.cs.indiana.edu/index.html) results in probable pathogenicity (mutation score of 0.57).

We present 2 sisters with motor neuron disease associated with a novel heterozygous *TBK1* LoF mutation, without family history of ALS-FTD, possibly due to incomplete penetrance, both affected in their 60s, in line with the reported late onset disease. One presented with bulbar-onset ALS, and the other with pure UMN involvement on clinical and neurophysiological examination. Primary lateral sclerosis (PLS) is a rare variant characterized by exclusive UMN involvement, usually with a more benign course than ALS [12]. To our knowledge, PLS associated to *TBK1* mutations was only reported in 2 patients from Spanish ancestry, but with a different *TBK1* mutation [13]. Patient 2 cannot be classified as PLS because she has not reached 4 years of disease progression yet, but considering the complete absence of LMN signs on a recent extensive neurophysiological investigation after more than 3 years of progression, she will probably be categorized as PLS briefly.

Our cases build on the variable phenotypical description of fALS due to TBK1 pathogenic mutations and support genetic testing for TBK1 not only in ALS but also in PLS cases with positive family history.

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