A study in a Turkish family with ataxia and points to MTCL1 as a candidate gene for autosomal ressesive cerebellar ataxia

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INTRODUCTION AND ABSTRACT

Spinocerebellar ataxias (SCAs) are heterogenous genetic disorders whose diagnostic evaluation remains challenging. In recent years, autosomal recessive spinocerebellar ataxia syndromes have been named SCAR. Many genes responsible for SCAR have been uncovered to date, so far 61 distinct autosomal recessive spinocerebellar ataxia syndromes and candidate genes described (1), and MTCL1 gene is one of them. Here, we present an 18-year-old female patient with spinocerebellar ataxia from a consanguineous family. We found a novel homozygous loss of function variant in the microtubule cross-linking factor 1 (MTCL1) gene that has recently been reported to be essential for the maintenance of Purkinje neurons in mouse models (2). Therefore, we suggest MTCL1 is a candidate gene for autosomal recessive spinocerebellar ataxias.

OBJECTIVES

Inherited ataxias are a group of highly heterogeneous neurological disorders representing a significant diagnostic challenge in clinical practice. We performed next-generation sequencing(NGS) in a case with progressive cerebellar ataxia of suspected autosomal ressesive(AR) inheritance. We found a novel homozygous microtubule cross-linking factor 1(MTCL1) loss of function variant in a 18-year-old patient. We propose MTCL1 as a candidate gene for AR cerebellar ataxia in humans.

MATERİALS AND METHODS

An 18-year-old female, born to consanguineous parents, suffered from uncoordinated gait and abnormal speech for a few years. The detailed physical examination revealed that she had dysarthria, intentional tremors in upper limbs, and dysmetria. Ophthalmological and cardiological evaluations (echocardiography) were normal and she had no hearing loss. While brain MRI showed cerebellar atrophy in the sagittal view, spinal MRI was normal. Also, no abnormality was found by Somatosensory Evoked Potential (SEP) test and Electromyography (EMG). According to the clinical presentations, physical examination, and MRI findings, she was considered to have hereditary ataxia. Initially, SCA Next Generation Sequencing (NGS) panel analysis was performed in another center, and no pathogenic mutation was detected. The patient presented as a sporadic case with a negative family history of ataxia. . AR inheritance was suspected based on the family history(the same mutation was detected in the mother and father) and early age of onset(<30 years. We performed NGS analysis with atax ia panel on genomic DNA from whole blood. The disease-causing variant was studied in all available family members by direct Sanger sequencing.

RESULTS

We found a novel homozygous MTCL1 loss of function variant c.49C>T(p.GLN17Ter) in the 18-year-old patient with progressive cerebellar ataxia, mild intellectual disability, episodic pain in the lower limbs. The same mutation was detected in the mother and father in the absence of the clinic.

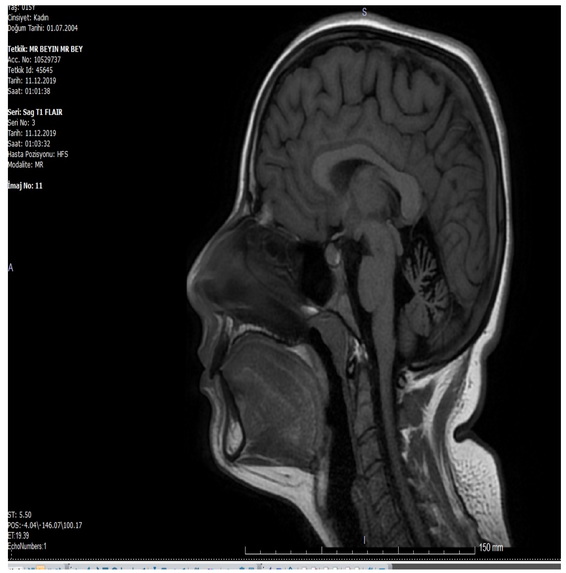

FIGURE 1 Sagittal T1-weighted magnetic resonance imaging (MRI) for a patient with the homozygous MTCL1 c.49C>T(p.GLN17Ter) variant showed isolated atrophy of the cerebellar vermis and perivermal region

CONCLUSİONS

In 2018, Krygier et al. presented a patient with spinocerebellar ataxia with a homozygous frameshift MTCL1 mutation (2), and this is the only case so far to suggest the association between MTCL1 with spinocerebellar ataxia in human. Here, we present an 18-year-old female patient with spinocerebellar ataxia from a consanguineous family. Whole exome sequencing (WES) revealed a homozygous loss of function (p.Gln17Ter) mutation in exon 3 of MTCL1 gene. Disruption of this gene caused spinocerebellar ataxia symptoms with Purkinje cell degeneration in mice (3). Therefore, we suggest MTCL1 is a candidate gene for autosomal recessive spinocerebellar ataxias.

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