Neurol Sci (2017) 38:2203–2207
DOI 10.1007/s10072-017-3049-8

BRIEF COMMUNICATION

SYNE1 related cerebellar ataxia presents with variable phenotypes in a consanguineous family from Turkey

E. Yucesan[1,2] · Sibel A. Ugur Iseri[1] · B. Bilgic[3] · Z. Gormez[4,5] · B. Bakir Gungor[4,6] · A. Sarac[4,7] · O. Ozdemir[1] · M. Sagiroglu[4,8] · H. Gurvit[3] · H. Hanagasi[3] · U. Ozbek[1,9]

Received: 8 March 2017 / Accepted: 21 June 2017 / Published online: 7 July 2017

Abstract *SYNE1* related autosomal recessive cerebellar ataxia type 1 (ARCA1) is a late-onset cerebellar ataxia with slow progression originally demonstrated in French-Canadian populations of Quebec, Canada. Nevertheless, recent studies on *SYNE1* ataxia have conveyed the condition from a geographically limited pure cerebellar recessive ataxia to a complex multisystem phenotype that is relatively common on the global scale. To determine the underlying genetic cause of the ataxia phenotype in a consanguineous family from Turkey presenting with very slow progressive cerebellar symptoms including dysarthria, dysmetria, and gait ataxia, we performed SNP-based linkage analysis in the family along with whole exome sequencing (WES) in two affected siblings. We identified a homozygous variant in *SYNE1* (NM_033071.3: c.13086delC; p.His4362GlnfsX2) in all four affected siblings. This variant presented herein has originally been associated with only pure ataxia in a single case. We thus present segregation and phenotypic manifestations of this variant in four affected family members and further extend the pure ataxia phenotype with upper motor neuron involvement and peripheral neuropathy. Our findings in turn established a precise molecular diagnosis in this family, demonstrating the use of WES combined with linkage analysis in families as a powerful tool for establishing a quick and precise genetic diagnosis of complex neurological phenotypes.

Keywords Autosomal recessive cerebellar ataxia · *SYNE1* · Peripheral neuropathy · Linkage analysis · Whole exome sequencing · E. Yucesan and S. A. Ugur Iseri contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s10072-017-3049-8) contains supplementary material, which is available to authorized users.

✉ Sibel A. Ugur Iseri
sibel.ugur@istanbul.edu.tr

1 Department of Genetics, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey

2 Present address: Institute of Life Sciences and Biotechnology, Bezmialem Vakif University, Istanbul, Turkey

3 Behavioral Neurology and Movement Disorders Unit, Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

4 Advanced Genomics and Bioinformatics Research Center (IGBAM), BILGEM, TUBITAK, Kocaeli, Turkey

5 Present address: Department of Software Engineering, Faculty of Engineering, Istinye University, Istanbul, Turkey

6 Present address: Faculty of Engineering, Abdullah Gul University, Kayseri, Turkey

7 Present address: Marmara Research Center, Genetic Engineering and Biotechnology Institute, TUBITAK, Kocaeli, Turkey

8 Present address: TUBITAK, BILGEM, UEKAE, Kocaeli, Turkey

9 Present address: Faculty of Medicine, Department of Medical Genetics, Acıbadem University, Istanbul, Turkey

Introduction

Autosomal recessive cerebellar ataxias (ARCA) are a rare, but heterogeneous group of inherited neurodegenerative disorders, in which cerebellar ataxia starting typically before the age of 20 years is the prominent clinical feature [1]. Cerebellar ataxia is typically accompanied by additional neurological findings including peripheral neuropathy, movement disorders, epilepsy, and cognitive deterioration [2]. The differential diagnosis of ARCA subtypes has been challenging due to presence of both overlapping phenotypes and increasing number of genes associated with ARCAs.

Among ARCAs, ARCA1 (MIM 610,743) is known as the pure recessive ataxia of Beauce as homozygous variations in synaptic nuclear envelope protein 1 (*SYNE1*) gene associated with ARCA1 were first reported in patients originating from the Quebec region of Beauce, Canada [3]. Since this original report, several *SYNE1* mutations have been reported for

patients from various ethnic groups, making *SYNE1* deficiency a global cause of recessive ataxia with a frequency approaching 6% in cohorts with presumably recessive inheritance [4–6]. These subsequent studies have also added new non-cerebellar features to the *SYNE1* ataxia phenotype, including motor neuron defects, brainstem dysfunction, and musculoskeletal abnormalities. All implicated mutations are almost exclusively truncating scattering throughout *SYNE1*, which is one of the largest genes in the human genome [5].

Herein, we ascertained a consanguineous family from Turkey with ARCA. Applying a parallel approach including linkage analysis along with whole exome sequencing (WES), we identified a pathogenic variation in *SYNE1,* segregating with the condition in the family.

Materials and methods

A consanguineous family from Turkey having four affected siblings along with three unaffected members has been followed-up for 10 years at the Behavioral Neurology and Movement Disorders Unit of the Neurology Department,

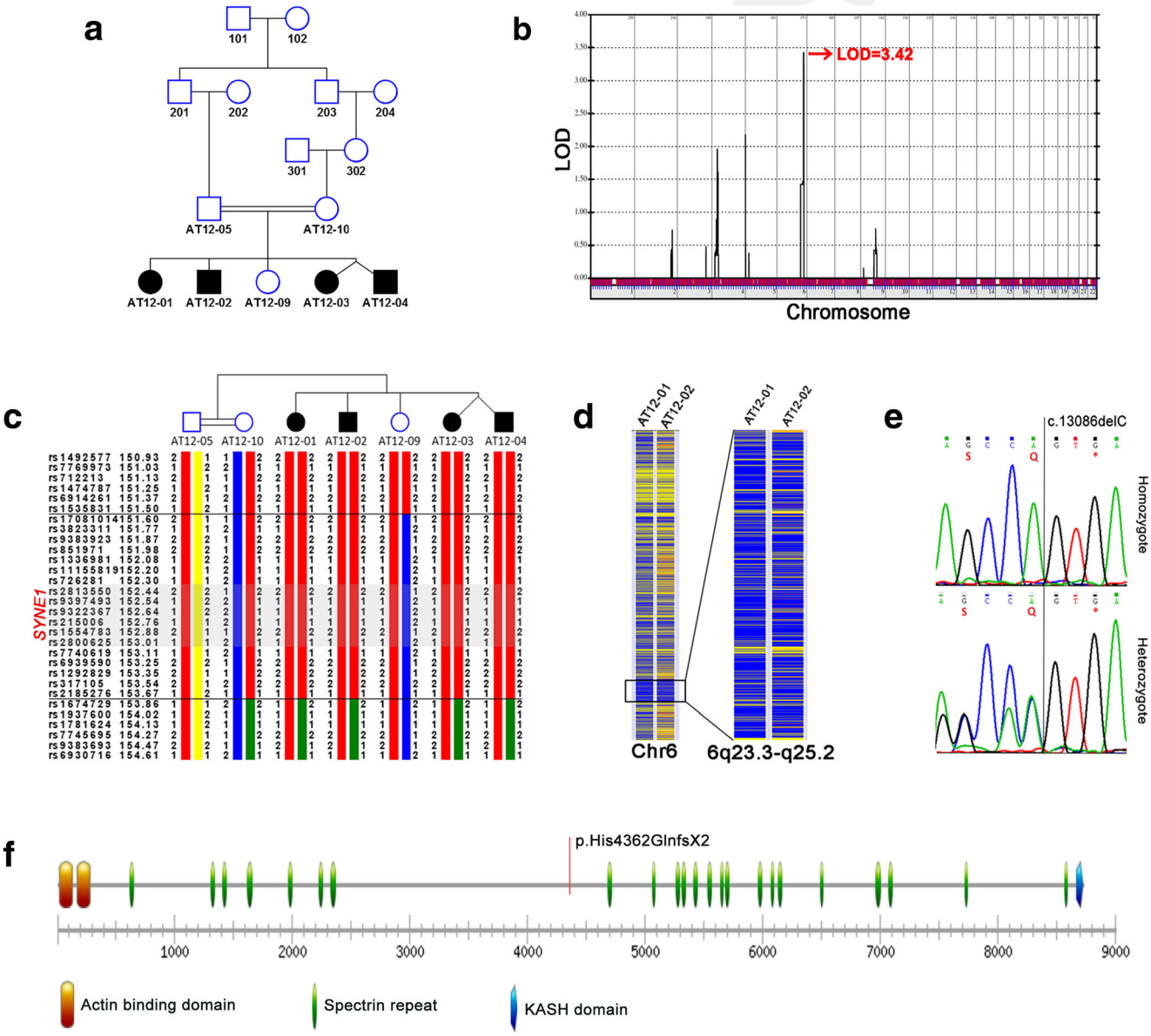

Fig. 1 Genetic analyses in the family. **a** Pedigree showing the degree of consanguinity. **b** Multipoint LOD scores in the family along the autosomes. **c** Haplotype analysis around the SNP-based linkage region. All four affected individuals are homozygous for an identical by descent haplotype that is colored in red. **d** HomSI analysis of WES data detects a shared ROH region in the two affected siblings at 6q23.3-q25.2. **e** Chromatograms showing NM_033071.3: c.13086delC both in homozygous and heterozygous form selected from the family. **f** The variation mapped at the protein level

Istanbul Faculty of Medicine, Istanbul University (Fig.1). Physical and neurological examinations were performed for all available family members and detailed information on family history was collected. Informed consents were obtained from all family members in accordance with Istanbul University, Istanbul Faculty of Medicine, Clinical Ethics Committee.

The genotyping data for all seven family members were produced via HumanCytoSNP-12 BeadChip array (Illumina) and subjected to whole genome logarithm of the odds (LOD) score analysis using the software package easyLINKAGE plus version 5.08 [7] assuming recessive inheritance with full penetrance. WES was performed for an affected sib pair selected from the family on an Illumina HiSeq-2000 system as described previously [8].

Results

Clinical characteristics

The index case (AT12–01) is a 43-year-old woman, who was admitted to our clinic at the age of 29 with progressively worsening unsteadiness of gait and speech disturbance. She started to slur her speech at the age of 26 and her gait problem started to appear 3 years after that. The severity of these symptoms progressed relatively slowly in the following years and she was still able to walk independently and her speech was intelligible at her last visit at the age of 42. In her neurological examination, there was significant gait ataxia and dysarthria and mild appendicular ataxia. Her deep tendon reflexes were brisk and bilateral Babinski sign was present. Her saccadic eye movements were normal and no nystagmus was observed. Magnetic resonance imaging (MRI) of the brain revealed global atrophy of the cerebellum mainly involving the vermis. Although her sensory examination was normal for light touch, proprioception, and vibration, sensory axonal polyneuropathy (SAP) was detected in an electromyoneurography (EMNG) study at the age of 41. Nerve conduction studies included ulnar, median, sural, and peroneal superficial nerves for sensory conduction and ulnar, median, tibial, and peroneal nerves for motor conduction. This study revealed axonal-type sensory neuropathy with reduction of sensory nerve action potential amplitude of sural and superficial peroneal nerves. Motor nerve conduction studies and electromyogram were normal. Interestingly, her ENMG performed at her first admission was found to be normal. There was no history of any chronic systemic and metabolic disease and any drug or substance abuse in her past medical history. Nevertheless, she was diagnosed as systemic lupus erythematous (SLE) presenting with arthritis at the age of 30 and treated with steroid and azathioprine in the

Table 1 Clinical characteristics of affected family members

	AT12–01	AT12–02	AT12–03	AT12–04
Sex	F	M	F	M
Age at onset	26	23	26	21
First detectable sign	Speech disturbance	Speech disturbance	Speech disturbance, unsteady gait	Speech disturbance, unsteady gait
Age at last examination	42	43	29	32
Progression	Dysarthria, gait and appendicular ataxia	Dysarthria, truncal and appendicular ataxia	Dysarthria, truncal and appendicular ataxia	Dysarthria, truncal and appendicular ataxia
Pyramidal signs	Brisk deep tendon reflexes and Babinski sign	Brisk deep tendon reflexes	–	–
Oculomotor findings	Normal	Normal	Normal	Normal
ENMG study	Normal (29 years) SAP (41 years)	Normal (43 years)	Normal (29 years)	No SAP (32 years)
MRI findings	Cerebellar atrophy	Cerebellar atrophy, chronic infarction in the MCA arterial territory (involving left PFC and adjacent white matter)	Cerebellar atrophy	Cerebellar atrophy
Other findings	SLE with arthritis, urinary incontinence, migrainous type headaches	None declared	Type 1 diabetes, hyperlipidemia, asymptomatic mitral valve prolapse, depression	None declared

ENMG electroneuromyography, *MCA* middle cerebral artery, *SAP* sensory axonal polyneuropathy, *SLE* systemic lupus erythematosus, *PFC* prefrontal cortex

following years. The clinical characteristics of the three affected siblings of this patient, who are a 41-year-old male and 33-year-old different sex fraternal twins, have been complied in Table 1.

Linkage analysis followed by WES identifies a homozygous frameshift variation in *SYNE1*

Genotyping results in the family demonstrated linkage to a 2.05 Mb region on chromosome 6q25.1-q25.2 between rs1535831 and rs1674729 with a multipoint LOD score approaching 3.42 (Fig.1). Parallel analysis of the WES data with the HomSI software was suggestive for a shared run of homozygosity (ROH) region of 18 Mb in two affected siblings encasing the smaller linkage interval (Supplementary Table 1). Among 26 genes that resided in the SNP derived linkage interval, only *SYNE1* encompassed a variant with a serious effect on protein as derived from WES data (*GRCh37* chr6:152,652,521delG, *GRCh38* chr6:152,331,386delG, NM_033071.3:c.13086delC; p.His4362GlnfsX2). Sanger sequencing of this variant along with haplotype inspection of the linkage region confirmed segregation of c.13086delC with the phenotype in the pedigree (Fig. 1). This variant has not still been annotated in public databases and also was not detected in 387 unrelated individuals screened from Turkey. We have therefore submitted this variant to the freely accessible NCBI ClinVar Database on July 2015 (mdi-5858).

Discussion

Using two unbiased genetic approaches, SNP-based linkage analysis and WES, we identified a variation in *SYNE1* as a cause for adult onset ataxia (age of onset between 21 and 26 years). Since *SYNE1* is one of the largest genes in the genome with 146 exons, studying it with conventional methods might be challenging. Our in-depth clinical and genetic analyses in this family manifesting only progressive cerebellar ataxia as the prominent clinical feature have led us to provide a genetic diagnosis as *SYNE1* related ARCA. The identified variation has recently been reported in a single case having pure ataxia from Germany with a Turkish origin [5]. Given the lack of mutational hotspots in this large gene and common ethnic origins of the patients, it is tempting to speculate that both that case and the family presented herein are originating from the same ancestor. Our study therefore, extends the pure cerebellar ataxia phenotype associated with *SYNE1* c.13086delC variant to four siblings, who are possibly relatives of the Turkish case in the original study. We have additionally detected non-cerebellar features, including upper motor neuron involvement (UMNI) in two siblings (brisk deep tendon reflexes and bilateral Babinski sign) and SAP in the index case. Although there were no clinical signs of SAP, electrophysiological signs of this feature were detected in the follow-up of the patient 12 years after her first ENMG study, which was normal. We underlay the importance of follow-up ENMG studies to determine the extent to which neuropathy is involved in patients with pathogenic *SYNE1* variations. Our results demonstrate variable expressivity for non-cerebellar features in ARCA1, where both frequently observed UMNI and rarely detected SAP are observed within the same family [5] [9].

Acknowledgements The authors are grateful to the family for participating in this study. This work was supported by the grants of Scientific Research Projects Coordination Unit of Istanbul University, the Scientific and Technological Research Council of Turkey (TUBITAK), and the Republic of Turkey Ministry of Development with grant reference numbers of ONAP-11021, UEKAE, BILGEM K030-T439, and Infrastructure Grant-2011 K120020, respectively. Biobanking support was given by Istanbul Development Agency (Project Number TR10/15/YNK/0093). EY and OO have been fellows of TUBITAK Project Number 113S331.

We highly appreciate the efforts of Monica Ann Malt, MSN, RN, and CPAN (Bezmialem Vakif University, Turkey) in language editing of this paper.

Compliance with ethical standards The authors declare no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Istanbul University, Istanbul Faculty of Medicine, Clinical Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Accordingly, informed consents were obtained from all family members.

Conflict of interest The authors declare that they have no conflict of interest.

Funding This work was supported by the grants of Scientific Research Projects Coordination Unit of Istanbul University, the Scientific and Technological Research Council of Turkey (TUBITAK), and the Republic of Turkey Ministry of Development with grant reference numbers of ONAP-11021, UEKAE, BILGEM K030-T439, and Infrastructure Grant-2011 K120020, respectively. Biobanking support was given by Istanbul Development Agency (Project Number TR10/15/YNK/0093). EY and OO have been fellows of TUBITAK Project Number 113S331.

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