

Letter to the Editor

When should we test patients with familial ataxias for SCA31? A misdiagnosed condition outside Japan?



The autosomal dominant spinocerebellar ataxias (SCAs) are a highly heterogeneous group of genetic diseases characterized by progressive gait ataxia and variable degrees of extracerebellar symptoms and signs. SCAs comprise a large number of unusual genetic disorders, and may be considered a diagnostic challenge. Genetics has a significant role to play in the etiology, and up to now, approximately 40 SCA subtypes have been described, and at least 32 different loci were identified [1]. As the knowledge of clinical and genetic features of SCAs is growing, the “What type of SCA should this patient tested for?” question becomes important before ordering a SCA diagnostic panel. Although whole-exome sequencing is a promising approach to search simultaneously for a large number of genetic conditions, it is usually ineffective to identify some SCA subtypes, since their mutations may lie in a noncoding genomic region or consist of large repeat expansions.

Spinocerebellar ataxia type 31 (SCA31), a late-onset cerebellar ataxia with or without hearing loss, is one of the most common inherited ataxia in Japan. To date, only two cases of SCA31 were described in other countries [2,3] and large European [4] and Taiwanese [5] population studies showed no SCA31 cases. Thus, SCA31 could be a misdiagnosed condition outside Japan.

In this article, we aimed to describe a Brazilian family with SCA31 and to provide clinical clues in order to request a specific genetic testing for this unusual SCA subtype outside Japan.

1. Case description

Three Brazilian siblings from Japanese ancestry with progressive familial ataxia were evaluated at the Ataxia Unit of the Universidade Federal de São Paulo. Proband was tested for a SCA panel (SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA17, and dentatorubral-pallidolusian atrophy – DRPLA). Long-range polymerase-chain reaction (PCR) amplification of genomic DNA using a primer pair spanning the SCA31 mutation site that includes penta-nucleotide (TGGAA)_n repeats and additional sequence analysis of the *puratrophin-1* gene (*PLEKHG4*) were performed as previously described [6,7].

Proband (III-6, Fig. 1A): a 66-year-old man presented with slow progressive cerebellar ataxia and mild dysarthria beginning 7 years ago. His parents (II-1 & 2, Fig. 1A) were born in Japan, one of the areas with a high SCA31 prevalence (Shikoku and Osaka). Two siblings (III-5 & III-10) had similar disease. Neurological examination revealed moderate global cerebellar ataxia (Video). He complained of bilateral hearing loss and audiogram showed moderate bilateral sensorineural deafness. Brain magnetic resonance imaging (MRI) disclosed mild cerebellar atrophy (Fig. 1C). He was negative for SCA1, SCA2, SCA3, SCA6, SCA10, SCA12, SCA17 and DRPLA. We suspected of SCA31

because of Japanese ancestry, late-onset cerebellar ataxia, and hearing loss. PCR reaction showed heterozygous expanded penta-nucleotide repeat insertion (Fig. 1B #III-6, black arrow) in the intron of *BEAN/TK2* gene, confirming the diagnosis of SCA31. In addition, the single nucleotide polymorphism –16C>T in the *PLEKHG4* gene, which is located close to the site of expansion, was also found.

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Patient 2 (III-5, Fig. 1A): a 67-year-old man had a similar phenotype, with progressive ataxia for the last 11 years. Examination disclosed pure cerebellar ataxia. Audiogram disclosed mild bilateral sensorineural deafness. Brain MRI showed mild cerebellar atrophy. Genetic test was also positive for SCA31 (Fig. 1B, #III-5).

Patient 3 (III-10, Fig. 1A): a 58-year-old man, also with similar phenotype for the last 3 years, presented with progressive ataxia. On examination, there was pure cerebellar ataxia. Audiogram was not performed. Brain MRI showed mild cerebellar atrophy. Genetic test was also positive for SCA31 (Fig. 1B, #III-10).

2. Discussion

SCA31 is a recently reported SCA subtype with a significant founder effect. The disease is caused by penta-nucleotide repeats containing (TGGAA)_n, (TAGAA)_n, and (TAAAA)_n, in an intronic region of *BEAN/TK2* gene located in chromosome 16q22.1. (TGGAA)_n is the only penta-nucleotide that segregated with the classical phenotype and was considered pathological [6]. Notably, we found that Brazilian patients also harbor heterozygous –16C>T single-nucleotide substitution in the *PLEKHG4* gene, which is not pathogenic or required for SCA31 diagnosis, but indicates that these subjects harbor the founder Japanese SCA31 haplotype [6,7]. In SCA31, RNA-mediated gain-of-function mechanism plays a role in pathogenesis, such as observed in myotonic dystrophy, fragile X-tremor ataxia syndrome, SCA8 and SCA10 [6].

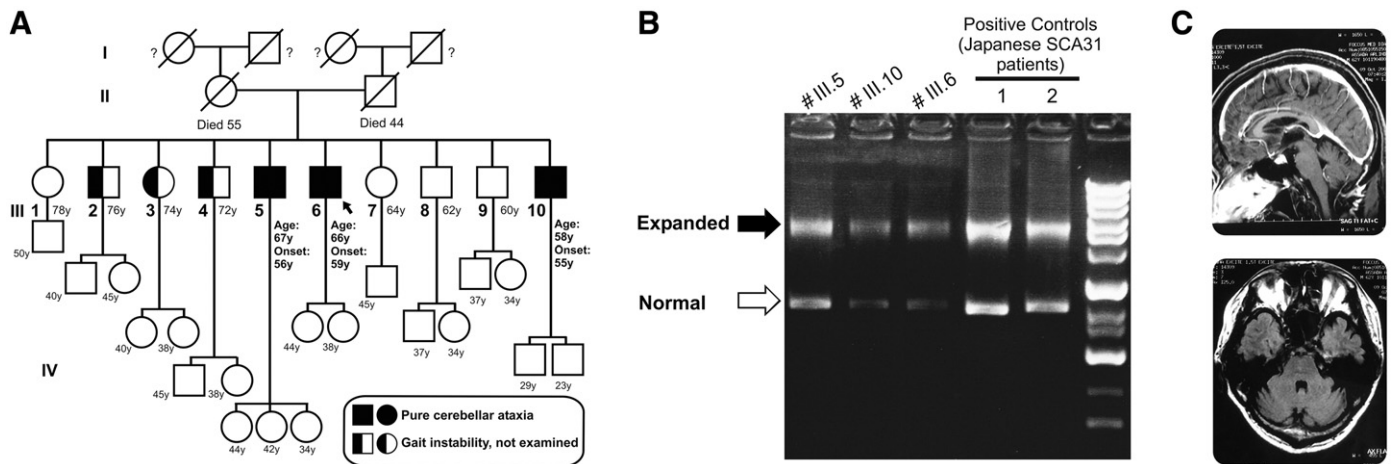


Fig. 1. (A): Pedigree of the SCA31 patients. (B): The result of PCR amplification using a primer pair spanning the SCA31 repeat mutation site [6]. The white arrow indicates PCR products corresponding normal-range repeats, and the black arrow indicates expansions. All three Brazilian subjects (#III-5, #III-6 and #III-10) harbor repeat expansion comparable to the ones in two Japanese positive controls (#1 and #2) reported previously [6]. (C): Brain MRI of the proband revealed mild cerebellar atrophy. The upper image is an enhanced sagittal T1 acquisition and the lower image is an axial FLAIR acquisition.

The most common SCAs in Japan are SCA3, SCA6 and SCA31, and DRPLA [4,8]. The cardinal features of SCA31 include a slowly progressive and late-onset (after the fifth decade) relatively pure cerebellar ataxia that might be associated with hearing impairment [6]. Neuroimaging usually discloses mild cerebellar atrophy (Fig. 1C), more pronounced in the superior vermis [9].

SCA31 was not found in large cohorts of undiagnosed autosomal-dominant cerebellar ataxia from Germany [4], France [4] and Taiwan [5]. To date, only two SCA31 cases were described outside Japan, one patient from Korea [2] and one from northern China [3]. Of note, they did not have Japanese ancestry and SCA31 may not be an ethnic-specific disease and may be misdiagnosed in different countries [3]. Therefore, this is the first report of SCA31 from the American continent. Interestingly, the phenotype described herein is very similar to those described in Japan, Korea and China: late onset cerebellar ataxia and hearing loss [2,3,6,7]. Considering our findings, patients with late-onset pure cerebellar ataxia from Japanese ancestry should be tested for SCA6 [10] and for SCA31 in Brazil. In this reported kindred, the symptoms were found in only one generation, which could mislead to autosomal recessive causes of ataxia, however it is most likely related to the late onset of the symptoms in autosomal dominant SCA31 and the premature death of proband's parents in their forties or fifties or to incomplete penetrance of SCA31 [3]. All three patients reported in our article had mild cerebellar atrophy (Fig. 1C), as described in other SCA31 patients.

In conclusion, our findings suggest that patients with familial late-onset pure cerebellar symptoms, variably associated with hearing impairment should be tested for SCA31 particularly if there is Japanese ancestry and negative test for SCA6. It is possible that the diagnosis of SCA31 is misdiagnosed outside Japan.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jns.2015.05.016>.

Conflict of interests

We have no conflict of interest.

Financial disclosure

We have nothing to disclose.

Ethical statement

Full consent was obtained from the patients for the case report and video publication. Our Ethics Committee approved this study.

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José Luiz Pedroso*
Agessandro Abrahao

Department of Neurology, Division of General Neurology and Ataxia Unit,
Universidade Federal de São Paulo, Brazil

*Corresponding author at: Department of Neurology and Neurosurgery,
Federal University of São Paulo, Botucatu Street, 740, Vila Clementino,
São Paulo, Brazil.

E-mail address: jlpedroso.neuro@gmail.com (J.L. Pedroso).

Kinya Ishikawa

Department of Neurology, Graduate School, Tokyo Medical and Dental
University, Tokyo, Japan

Salmo Raskin

Group for Advanced Molecular Investigation (NIMA), Graduate Program in Health Sciences (PPGCS), Center for Biological and Health Sciences (CCBS), Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, Paraná, Brazil
Genetika – Centro de Aconselhamento e Laboratório de Genética, Curitiba, Paraná, Brazil

Paulo Victor Sgobbi de Souza

Wladimir Bocca Vieira de Rezende Pinto
Department of Neurology, Division of General Neurology and Ataxia Unit, Universidade Federal de São Paulo, Brazil

Pedro Braga-Neto

Department of Neurology, Division of General Neurology and Ataxia Unit, Universidade Federal de São Paulo, Brazil
Center of Health Sciences, Universidade Estadual do Ceará, Ceará, Brazil

Marcus Vinicius Cristino de Albuquerque

Department of Neurology, Division of General Neurology and Ataxia Unit, Universidade Federal de São Paulo, Brazil

Hidehiro Mizusawa

Department of Neurology, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Orlando G.P. Barsottini

Department of Neurology, Division of General Neurology and Ataxia Unit, Universidade Federal de São Paulo, Brazil

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