Spinocerebellar Ataxia 42: A New Entity in Indian Subcontinent

Dear Sir,

Spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders involving the cerebellum or its connections. Brainstem, spinal cord and cranial nerve nuclei may also be affected.[1] They cause progressive cerebellar ataxia. Other features like nystagmus, slow saccades, dysarthria, or extracerebellar signs may be present. Disease onset is usually between 30-50 years of age in the autosomal dominant SCAs. To the best of our knowledge, 48 subtypes of SCAs are described till date.[2]

SCA 42 is a rare subtype of SCA. The causative gene mutation for SCA 42 i.e., CACNA1G was first described in 2015.[3,4] We report a case of SCA 42 presenting with pan cerebellar syndrome, pyramidal features and positive family history. Clinical exome sequencing identified a heterozygous missense variant c.5144G > A in CACNA1G gene suggestive of Spinocerebellar ataxia 42. To the best of our knowledge, this is the second genotypically proven family from Indian subcontinent. There is one family reported from India by Mehta *et al*. with a different variant (c.6077C > T).[5]

A 39-year-old male presented with insidious onset, gradually progressive gait ataxia since 19 years of age. He was born of non-consanguineous marriage. His younger sister aged 35 years old had similar complaints since 20 years of age. No other family members were affected [Figure 1]. Higher mental functions were normal. Speech was dysarthric [Video 1]. There was no nystagmus. Pursuits and saccades were normal. Motor examination showed mild (modified Ashworth scale grade 1) spasticity in lower limbs with bilateral extensor plantar response. Sensory examination was normal. Cerebellar signs were present in both upper and lower limbs. Gait was ataxic [Video 2]. MRI brain with spinal cord screening showed moderate cerebellar atrophy with normal spinal cord [Figure 2]. His younger sister had mild dysarthria and gait ataxia. Rest examination was normal. Considering the age of onset, clinical presentation, positive family history, and MRI findings, a diagnosis of spinocerebellar ataxia was considered. Spinocerebellar ataxia panel for repeat expansion (SCA 1,2,3,6,7,10 and 12) by PCR was negative. Other work up i.e., TSH, VDRL, HIV, lipid profile, fundus, 2D echo, nerve conduction study was normal.

In spite of age of onset being 15 to 20 years, there was only mild progression noticed in both the siblings in fourth decade.

Table 1: Clinical characteristics of SCA 42 patients in different reports

Study	Kimura, *et al*.[1]	Coutelier, *et al*.[3]	Morino, *et al*.[4]	Mehta, *et al*.[5]	Li, *et al*.[9]	Our case
Number of patients	2 Japanese families-3 patients	3 French families-10 patients	2 Japanese families-15 patients	2 siblings	A family of 3 patients	2 siblings
Age of onset	35-36 years	9-78 years	20-70 years	15 years	43-60 years	15-20 years
Cerebellar features						
Main symptom	Gait instability	Gait instability	Gait instability	Gait instability	Gait instability	Gait instability
Dysarthria	++	++	++	++	++	++
Ocular signs	Saccadic pursuit	Saccadic pursuit	Horizontal nystagmus	No	No	No
Extracerebellar features						
Pyramidal signs	No	5 out of 10 patients	No	No	No	No
Movement disorder	No	Tremors in 1 patient	Tremors in 2 patients	Chorea, dystonia in both siblings	No	No
Cognitive impairment	No	3 out of 10 patients	No	In both siblings	No	No
Depression	No	2 out of 10 patients	No	No	No	No
Peripheral neuropathy	No	3 out of 10 patients	No	In both siblings	No	No

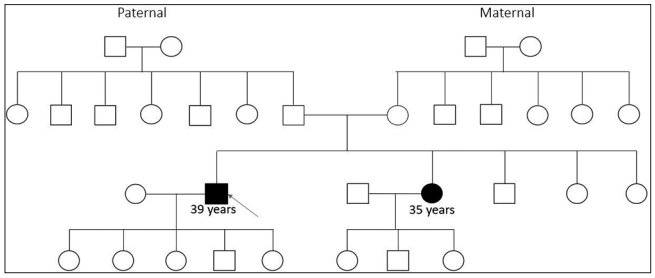

Figure 1: Pedigree chart of family with SCA 42

Hence, the possibility of autosomal dominant (AD) SCA with point mutation was considered. Clinical exome sequencing for AD ataxias was conducted.

Nextgeneration sequencing (NGS) was performed using a custom Clinical Exome Panel (MedGenome Labs) covering coding exons and flanking intronic sequences of >6800 genes associated with known inherited diseases. Genomic DNA was used for the library preparation for NGS and sequenced on the Hi Seq platform (Illumina). The sequences obtained were aligned to human reference genome (GRCh37/hg19) using Sentieon aligner.[6] Gene annotation of the variants was performed using VEP program[7] against the Ensembl release 91 human gene model. American College of Medical Genetics and Genomics (ACMG) guidelines were followed for variant classification.

A heterozygous missense variant c.5144G > A in exon 29 of the CACNA1G gene was detected. This results in the amino acid substitution of Histidine for Arginine at codon 1715 (p.Arg1715His; ENST00000359106.5). The in-silico predictions of the variant are probably damaging by polyphen-2 (HumDiv) and damaging by SIFT, LRT and Mutation Taster2. The c.5144G > A (p.Arg1715His) variant has not been reported in the 1000 genome, ExAC and MedGenome internal databases. The mutation is classified as pathogenic and is suggestive of SCA 42. This variant c.5144G > A has been previously reported from Japanese and French people, but not from Indian subcontinent. Hence, this mutation could be a founder mutation.

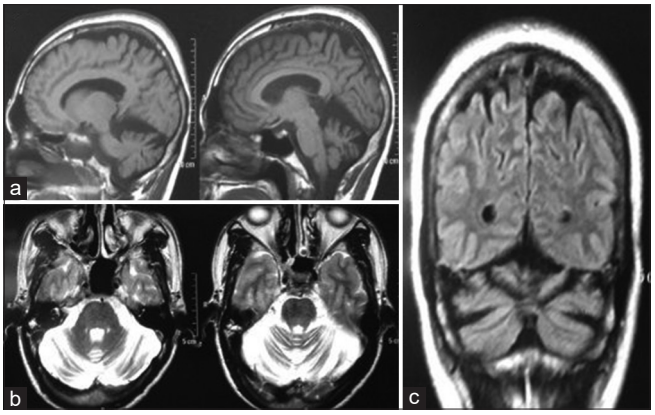

Figure 2: MRI images (a) T1 sagittal, (b) T2 axial and (c) FLAIR coronal of the patient showing moderate pan cerebellar atrophy

The observed variation lies in the ion transport domain of the voltage-dependent calcium channel protein Cav3.1.

CACNA1G encodes the T-type calcium channel Cav3.1. Cav3.1 is widely expressed in the brain, especially cerebellum and inferior olivary nucleus. Cav3.1 plays a predominant role in the regulation of membrane potential and modulation of calcium signaling pathways.[8] The mutation in the CACNA1G gene induces amino acid change in voltage sensor S4 segment of domain IV in Cav3.1. This results in decreased neuronal excitability in deep cerebellar nuclei. Also, $Ca2^{+}$ homeostasis is disrupted leading to activation of toxic cascades. This causes death of Purkinje cells and cerebellar atrophy.[8] These findings indicate that SCA42 is a channelopathy.[3,8]

SCA 42 was first described by Coutelier *et al.*[3] in 3 unrelated French families and by Morino *et al.*[4] in two Japanese families. Li *et al.* reported a Chinese family of 3 affected individuals.[9] There is wide variation in age of onset. In the study by Coutelier *et al.*, age of onset varied from 9-78 years.[3] Most patients have slowly progressive, mild to moderate cerebellar ataxia. Extracerebellar features like pyramidal signs, cognition impairment, movement disorders, peripheral neuropathy,

depression etc., are seen in a few cases [Table 1]. In most reports, MRI showed cerebellar, especially vermis atrophy.[3]

Recently, Mehta *et al*. reported SCA 42 in an Indian family.[5] The affected siblings presented in second decade with gait ataxia, cognitive decline, choreiform movements, and dystonia. Our patients had onset in the second decade with very slowly progressive course. There was only mild ataxia with dysarthria and mild pyramidal findings.

CACNA1G gene mutation is also known to cause infantile onset syndromic cerebellar ataxia. The disease manifests in pediatric age group with features like cerebellar ataxia, psychomotor and speech delay, intellectual disability, ectodermal, ophthalmologic features, and facial dysmorphism.[10]

SCA 42 is a very slowly progressive cerebellar ataxia accompanied with minimal extracerebellar features.[1,3,4,9] However, in recently reported case from south India, extracerebellar features were prominent.[5] There are few reports worldwide. To the best of our knowledge, this is the second report of genetically proven SCA 42 with a different variant from Indian subcontinent. Further studies are needed to elaborate the clinical characteristics and genotype-phenotype correlation of SCA 42. In view of very slow progression, it has a good prognosis. Genetic diagnosis helps in alleviating patient and family members' anxiety. Early physiotherapy/balance training exercises can improve quality of life of these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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