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A Novel Case of SCA42 Masquerading as SCA12 in Clinical Presentation

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ABSTRACT

Spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders involving the cerebellum or its connections. 48 subtypes of SCAs are described till date. To the best of our literature knowledge SCA42 masquerading as SCA12 in clinical presentation has never been reported. We reported a novel case of SCA42 masquerade as SCA12 in clinical presentation with predominant hand tremors followed by ataxic gait. A 65-year-old male patient presented with history of predominant hand tremors since past 5 years followed by ataxic gait. He had a family history of ataxia (mother, mother brother, and sister). Vermian atrophy, bilateral superior cerebellar peduncle hyperintensity, and mild brainstem atrophy were detected in MRI. The whole exome sequencing test of patient identified the heterozygous missense variant "c.6764A>Glp.Gln2255Arg" detected in the CACNA1G gene on chromosomal position chr17:50626381:A>G that can leads to a change in amino acid from Glutamine to Arginine at codon 2255. The whole exome sequencing of patient's mother's sister's son identified the autosomal dominant heterozygous triple nucleotide "CAG" repeat number of approximately 54 ± 4 in the PPP2R2B gene that can leads to pathogenic SCA12 expression. These findings emphasize the fact that SCA42 could masquerade as SCA12 in clinical presentation could be due to pathogenic SCA12 expression in the same family member. In conclusion, we reported the first novel case from Indian subcontinent that the heterozygous missense variant "c.6764A>Glp.Gln2255Arg" detected in the CACNA1G gene on chromosomal position chr17:50626381:A>G in 65-year-old male patient could masquerade as SCA12 in clinical presentation with clinical features of predominant hand tremors followed by ataxic gait.

Keywords: *Spinocerebellar ataxia; SCA42; SCA12; Hand tremors; Ataxic gait; CAG repeat.*

Introduction

Spinocerebellar ataxias (SCAs) comprise a diverse group of neurodegenerative disorders that primarily affect the cerebellum and its associated neural pathways. In addition to cerebellar involvement, the brainstem, spinal cord, and cranial nerve nuclei may also be affected [1]. These disorders are characterized by progressive cerebellar ataxia and may be accompanied by manifestations such as nystagmus, slow saccadic eye movements, dysarthria, and other extracerebellar features. The principal clinical manifestations of SCAs include cerebellar ataxia, ophthalmoplegia, cognitive dysfunction, and slurred speech. In autosomal dominant forms of SCA, symptom onset generally occurs between 30 and 50 years of age. The estimated prevalence of SCAs is approximately 2.7 cases per 100,000 individuals [2]. To date, 48 SCA

subtypes have been identified [3]. The distribution of the more prevalent SCA subtypes across different Asian countries is depicted in Figure 1 [4].

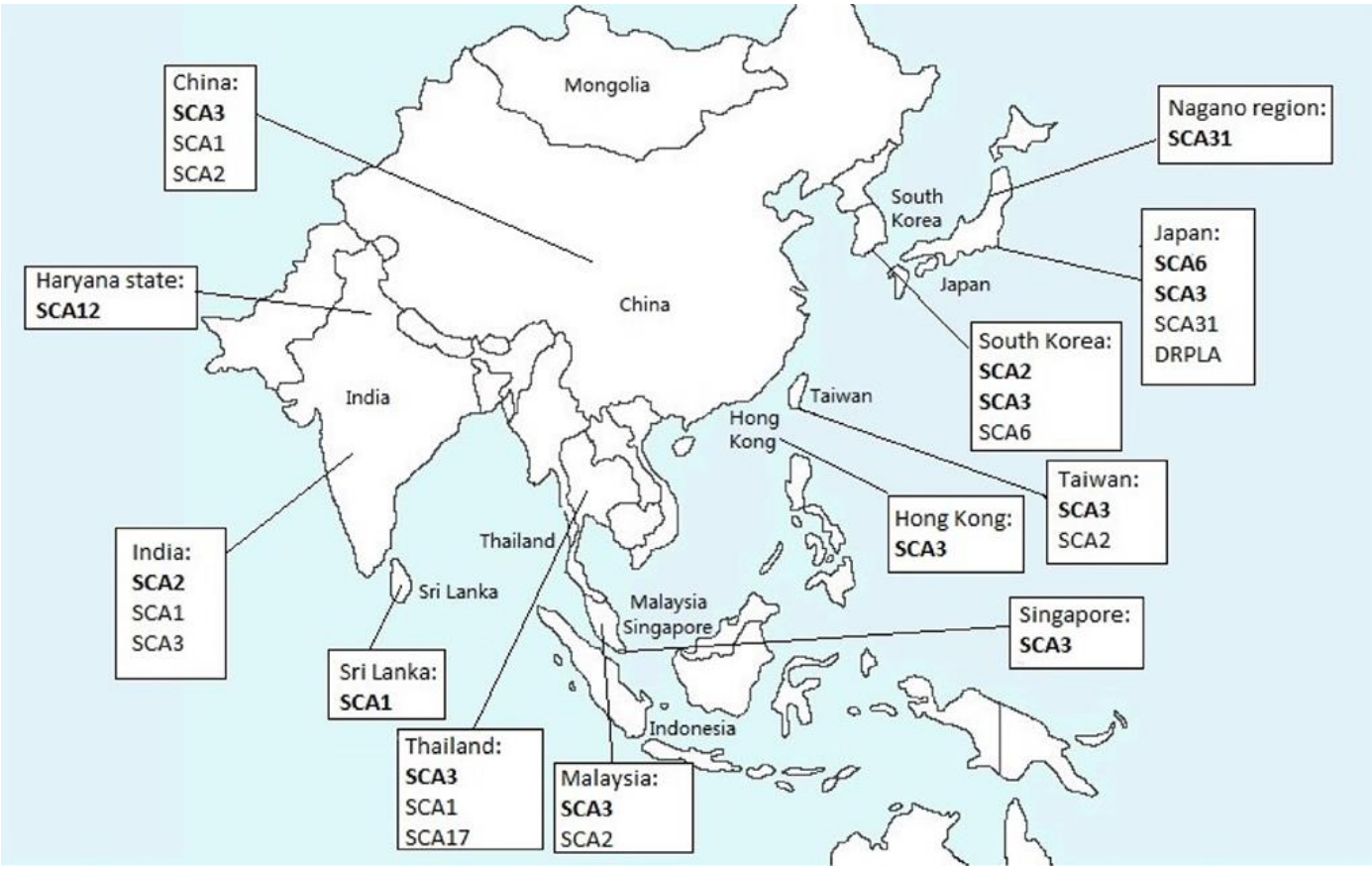

Figure 1. Illustration of common SCAs in Asian countries

Spinocerebellar ataxia type 42 (SCA42) is a rare subtype of SCA caused by pathogenic variants in the calcium voltage-gated channel subunit alpha1 G (*CACNA1G*) gene and was initially described in 2015 [5-7]. Among the identified variants, the c.5144G>A substitution results in an arginine-to-histidine amino acid change (p.Arg1715His) within the S4 voltage-sensing segment of the CaV3.1 T-type voltage-gated calcium channel, thereby altering channel function [8]. Spinocerebellar ataxia type 12 (SCA12) is a rare, progressive neurological disorder inherited in an autosomal dominant pattern and is caused by mutations in the *PPP2R2B* gene. It has been reported predominantly among individuals belonging to the Agarwal community in India. The disorder typically presents during the fourth decade of life with action tremor involving the upper limbs. As the condition advances, affected individuals invariably develop cerebellar ataxia. In the later stages of the disease, additional manifestations such as hyperreflexia, parkinsonism, psychiatric disturbances, and cognitive decline may become evident [9].

To the best of our literature knowledge SCA42 masquerading as SCA12 in clinical presentation has never been reported.

Case Presentation

A 65-year-old man presented with a five-year history of predominantly hand tremors since past 5 years, followed by the development of an ataxic gait (Video 1). His family history was significant for hereditary ataxia affecting his mother, maternal uncle, and sister. Neurological examination revealed slow saccadic eye movements without nystagmus, scanning dysarthria, postural and action tremors of the hands, limb incoordination, and a broad-based gait. Cognitive function was normal (MMSE 30/30). Magnetic resonance imaging (MRI) showed no evidence of the hot cross bun sign, crab sign, or dentate nucleus calcification. However, vermian atrophy, bilateral hyperintensities of the superior cerebellar peduncles, and mild brainstem atrophy were observed (Figure 2).

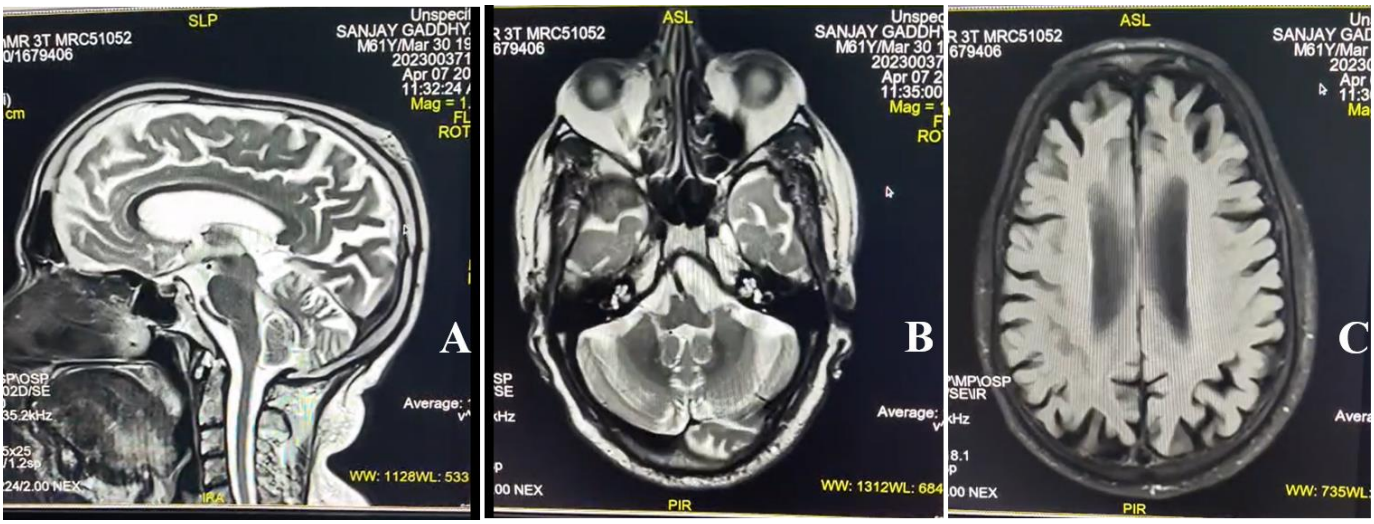

Figure 2: MRI image showing Vermian atrophy (A), bilateral superior cerebellar peduncle hyperintensity (B), and mild brainstem atrophy (C).

The patient subsequently underwent whole-exome sequencing (WES). Analysis identified a heterozygous missense variant, "c.6764A>Glp.Gln2255Arg" in the *CACNA1G* gene located at chromosomal position chr17:50626381>G. The identified variant had a sequencing depth of 45X and was located in exon 38 of transcript NM_018896.5, resulting in the substitution of glutamine by arginine at codon 2255 (Table 1). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this variant was classified as a Variant of Uncertain Significance (VUS) based on the criteria PM2 and PP2, in conjunction with the patient's phenotypic characteristics. No clinically significant copy number variations (CNVs) or mitochondrial DNA (mtDNA) variants were detected.

Table 1: Sequence variants related to phenotype

Gene (Transcript)	Location	DNA/Protein Change	Zygosity	Inheritance	Classification	Associated Disease/OMIM
CACNA1G (+) NM_018896.5	Exon 38	c.6764A>G p.Gln2255Arg	Heterozygous	Autosomal Dominant	Uncertain Significance	Spinocerebellar ataxia 42 (#616795)

The WES performed in the patient's mother's sister's son demonstrated an autosomal dominant heterozygous expansion of approximately 54 ± 4 CAG repeats within the *PPP2R2B* gene (Table 2). This expanded CAG repeat is consistent with SCA12, an autosomal dominant spinocerebellar ataxia caused by pathogenic expansion of more than 32 CAG repeats in the promoter region of the *PPP2R2B* gene. The identified repeat expansion was interpreted as pathogenic.

Table 2: Sequence abnormalities related to phenotype.|

Gene (Transcript)	Disease (OMIM)	Inheritance	Mutation type	Normal/Wild type repeats	No. of repeats detected	CAG repeated status
PPP2R2B NM_181678.2	SCA12 (#604326)	Autosomal dominant	Triple nucleotide repeats (CAN)n	[24_≤32]	[17_54±4]	Pathogenic

The clinical course in the 65-year-old patient, characterized initially by predominant hand tremor followed by progressive gait ataxia, suggests that SCA42 may clinically mimic SCA12. This phenotypic overlap may be attributable to the coexistence of pathogenic SCA12 associated genetic alterations within the same family.

Discussion

SCA42 was initially identified by Coutelier et al., in three unrelated French families [5], followed by the description of two Japanese families by Morino et al., [6]. Subsequently, Li et al., documented three affected members from a Chinese family carrying the disease [10]. The majority of reported patients exhibit slowly progressive cerebellar ataxia of mild-to-moderate severity. Although the disorder predominantly affects the cerebellum, a subset of patients may also develop extracerebellar manifestations, including pyramidal signs, cognitive impairment, movement disorders, peripheral neuropathy, and depression [11]. Neuroimaging findings in most published cases have demonstrated cerebellar atrophy, particularly involving the vermis [5]. In contrast, our patient did not exhibit several of these commonly reported clinical manifestations. More recently, Mehta et al., described SCA42 in an Indian family in which the affected siblings developed symptoms during the second decade of life, presenting with gait ataxia, cognitive decline, choreiform movements, and dystonia [12]. In comparison, our patient became symptomatic in the sixth decade and lacked features such as cognitive decline, choreiform movements, and dystonia as reported by Mehta et al.

The first description of SCA12 was reported by Holmes et al., who characterized the clinical and genetic spectrum in ten affected members of a German-American family. In that family, hand tremor represented the earliest manifestation in most affected individuals and was followed by gradually progressive cerebellar dysfunction as the disease advanced [13]. A similar clinical course was observed in our patient, who initially developed predominant hand tremors that persisted for five years before the onset of gait ataxia. Subsequently, Fujigasaki et al., evaluated 247 patients with cerebellar ataxia and identified only one family of Indian origin carrying a pathogenic *PPP2R2B* mutation [14]. Later, Srivastava et al., reported five unrelated Indian families with SCA12 caused by *PPP2R2B* mutations, with a mean age at disease onset of 37.2 years (range, 26–50 years). Clinical information from six affected individuals showed that expanded alleles ranged from 55 to 69 CAG repeats, while three asymptomatic carriers harbored repeat lengths of 55, 55, and 66 repeats, respectively. In all affected individuals, hand tremor was the presenting symptom and was followed by the development of cerebellar ataxia [15]. These observations closely resemble the findings in our patient. Furthermore, whole-exome sequencing performed in the patient's mother's sister's son demonstrated an expanded *PPP2R2B* allele containing approximately 54 CAG repeats, supporting the similarity between our case and previously reported SCA12 pedigrees.

Literature reports evidenced that SCA12 was associated with mild-to-moderate cerebellar atrophy, cerebral cortical atrophy, ventriculomegaly with or without subcortical white matter abnormalities, and loss of Purkinje cells [13,14,16,17]. The cerebellar vermis is generally more severely affected than the cerebellar hemispheres, whereas degenerative involvement of the brainstem and basal ganglia has rarely been reported [18]. In our patient, neuroimaging demonstrated vermian atrophy together with bilateral superior cerebellar peduncle hyperintensity and mild brainstem

atrophy. While the presence of vermian atrophy is consistent with previously described imaging features of SCA12, the accompanying brainstem abnormalities further emphasize the unusual neuroimaging profile observed in this case.

Based on the findings of this case, it may be postulated that the familial presence of pathogenic SCA12 could have influenced the clinical phenotype associated with the heterozygous missense variant "c.6764A>Glp.Gln2255Arg" identified in the *CACNA1G* gene at chromosomal position chr17:50626381>G in this 65-year-old patient. This phenotypic overlap may have resulted in SCA42 presenting with clinical features resembling SCA12, characterized by an initial presentation of predominant hand tremors for five years followed by the development of gait ataxia.

In conclusion, to the best our literature this is the first novel case reported from Indian subcontinent that the heterozygous missense variant "c.6764A>Glp.Gln2255Arg" detected in the *CACNA1G* gene on chromosomal position chr17:50626381:A>G in 65-year-old male patient could masquerade as SCA12 in clinical presentation with clinical features of predominant hand tremors followed by ataxic gait.

Patient Consent Declaration

Authors hereby declare that they have obtained patient consent.

Conflict of Interest

None

Funding

None to declare.

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