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A Novel De Novo STUB1 Variant Associated Spinocerebellar Ataxia 48 from Southern India: Case Report

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ABSTRACT

Autosomal dominant spinocerebellar ataxia type 48 (SCA48) is a newly identified subtype of SCA, marked by early onset of ataxia and cognitive impairment, and is associated with mutations in the STIP1 homology and U-box-containing protein 1 (STUB1) gene. We reported a case of novel de novo STUB1 variant cause of SCA48 presented with subacute ataxia with broad-based gait, mild incoordination of limbs, and mild dysarthria in 50-year-old female patient. Patient has no familial history of similar illness or other neurologic disorders. She did not have other abnormal movements such as parkinsonism, dystonia, chorea, or myoclonus. She had normal cognitive function. Patient's Scale for the Assessment and Rating of Ataxia (SARA) score was 7. Tendon reflexes were normal. Serum autoimmune encephalitis and paraneoplastic neuronal antibodies tests were negative. Sensory and plantar flexors were normal. Serum autoimmune encephalitis and paraneoplastic neuronal antibodies work-ups were negative. Brain magnetic resonance imaging (MRI) indicated mild cerebellar atrophy, small vessel ischemic changes, and calcified granuloma in left frontal region with no surrounding perilesional oedema. A nerve conduction study indicated no evidence of peripheral neuropathy or other abnormalities. The whole exome sequencing test identified the heterozygous missense variant "c.206G>C; p.Cys69Ser," detected in the STUB1 gene on chromosomal position chr16:681198:G>C. This variant is noted to have a total depth of 74X. It is located in exon 2 of the transcript NM_005861.4 and it leads to a change in amino acid from Cysteine to Serine at codon 69. The detected STUB1 gene "c.206G>C; p.Cys69Ser," variant in our case of 50-year-old female has not been previously reported among Indian population. In conclusion, we reported the unusual, uncommon case of SCA48 caused due to a novel de novo STUB1 gene variant "c.206G>C; p.Cys69Ser," in the chromosomal position chr16:681198:G>C led to a change in amino acid from Cysteine to Serine at codon 69 in 50-year-old female patient from southern India presented with clinical conditions such as subacute ataxia with broad-based gait, mild incoordination of limbs, and mild dysarthria.

Keywords: *Spinocerebellar ataxia; SCA48; STUB1 gene; Subacute ataxia; Cysteine; Serine.*

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Introduction

Spinocerebellar ataxia (SCA) represents a group of autosomal dominant, progressive neurodegenerative disorders marked by symptoms such as ataxia, gait instability, dysmetria, and dysarthria [1]. To date, approximately 50 distinct SCA subtypes have been described, each linked to mutations in various genes. These disorders can follow different inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked transmission [2]. Expanded CAG trinucleotide repeats (polyglutamine or polyQ) are responsible for most SCAs (40%–60%), while a smaller proportion (3%–5%) is attributed to other repeat expansions or point mutations [3,4]. Despite these discoveries, the underlying genetic cause remains unidentified in 30%–48% of patients [4]. The overall prevalence of SCA at the population level remains uncertain but has been estimated at approximately 2.7 per 100,000 individuals [5].

SCA48 is a recently discovered and rare subtype of SCA, initially described in a Spanish family. It is distinguished by early-onset cerebellar cognitive-affective syndrome followed by progressive spinocerebellar ataxia [1]. The clinical spectrum includes ataxia, cognitive decline, psychiatric manifestations, and diverse movement abnormalities that can be either hypo- or hyperkinetic, along with positive pyramidal signs, highlighting the heterogeneous nature of the disorder [6]. SCA48 results from mutations in the STIP1 homology and U-box-containing protein 1 (*STUB1*) gene and exhibits an autosomal dominant mode of inheritance (OMIM 607207) [1]. Mutations in the same gene were previously linked to autosomal recessive spinocerebellar ataxia type 16 (*SCAR16*), which shares overlapping clinical features with SCA48 [7].

To date, the ClinVar database lists 10 pathogenic, 4 likely pathogenic, and 2 variants of uncertain significance in the *STUB1* gene [8], with most reports originating from the Mediterranean region [9]. Only a single de novo *STUB1* variant–related case of SCA48 has been reported in Germany [10], and Choi et al. later described the first such case in Korea [11]. To the best of our knowledge, there have been no previous reports of de novo *STUB1* variant–associated SCA48 cases from India.

Here, we describe the case of SCA48 associated with a de novo *STUB1* variant in a 50-year-old woman presenting with subacute-onset ataxia, broad-based gait, mild limb incoordination, and mild dysarthria.

Case Presentation

A 50-year-old female with history of subacute ataxia with broad-based gait, mild incoordination of limbs, and mild dysarthria visited our neurology clinic. The symptoms have slowly progressed over 5 months, and their daily activities were affected by gait disturbance and cognitive decline. A neurologic examination revealed gait ataxia, dysarthria, and incoordination of the bilateral limbs. Patient has no familial history of similar illness or other neurologic disorders. Sensory and plantar flexors were normal. The patient demonstrated broad-based ataxic gait and poor balance with tandem gait (Video 1) and scored 7 on the Scale for Assessment and Rating of Ataxia (SARA). She did not have other abnormal movements such as parkinsonism, dystonia, chorea, or myoclonus. Tendon reflexes were normal. Serum autoimmune encephalitis and paraneoplastic neuronal antibodies work-ups were negative.

Brain magnetic resonance imaging (MRI) indicated mild cerebellar atrophy, small vessel ischemic changes, and calcified granuloma in left frontal region with no surrounding perilesional oedema (Figure 1). A nerve conduction study indicated no evidence of peripheral neuropathy or other abnormalities. The patient had normal cognitive function (MMSE and MOCA score were within normal limits).

Whole Exome Sequencing

Patient was referred for whole exome sequencing. Nucleic acid (DNA) was extracted from peripheral blood, using standard Qiagen nucleic acid isolation kits. Library was prepared as per instruction manual of Twist 2.0 Exome kit, including mitochondrial genome and sequencing was performed using Illumina NovaSeq X Plus platform as per user manual. The sequencing reads QC, mapping on hg38 human reference genome, variant calling (SNVs, small InDels) was carried out using illumina dragen v4.0. Annotation and interpretation were done considering information available in different databases like OMIM, ClinVar (v20220416), dbSNP (v155), 1000 Genomes (v5.20130502), ExAC (r0.3.1), gnomAD (v2.1.1), ESP (6500) and insilico prediction of variant impact on structure and function of proteins using Revel, MutationTaster, PolyPhen-2 and SIFT. Relevant variants were reported based on American College of Medical Genetics and Genomics (ACMG) standards and guidelines.

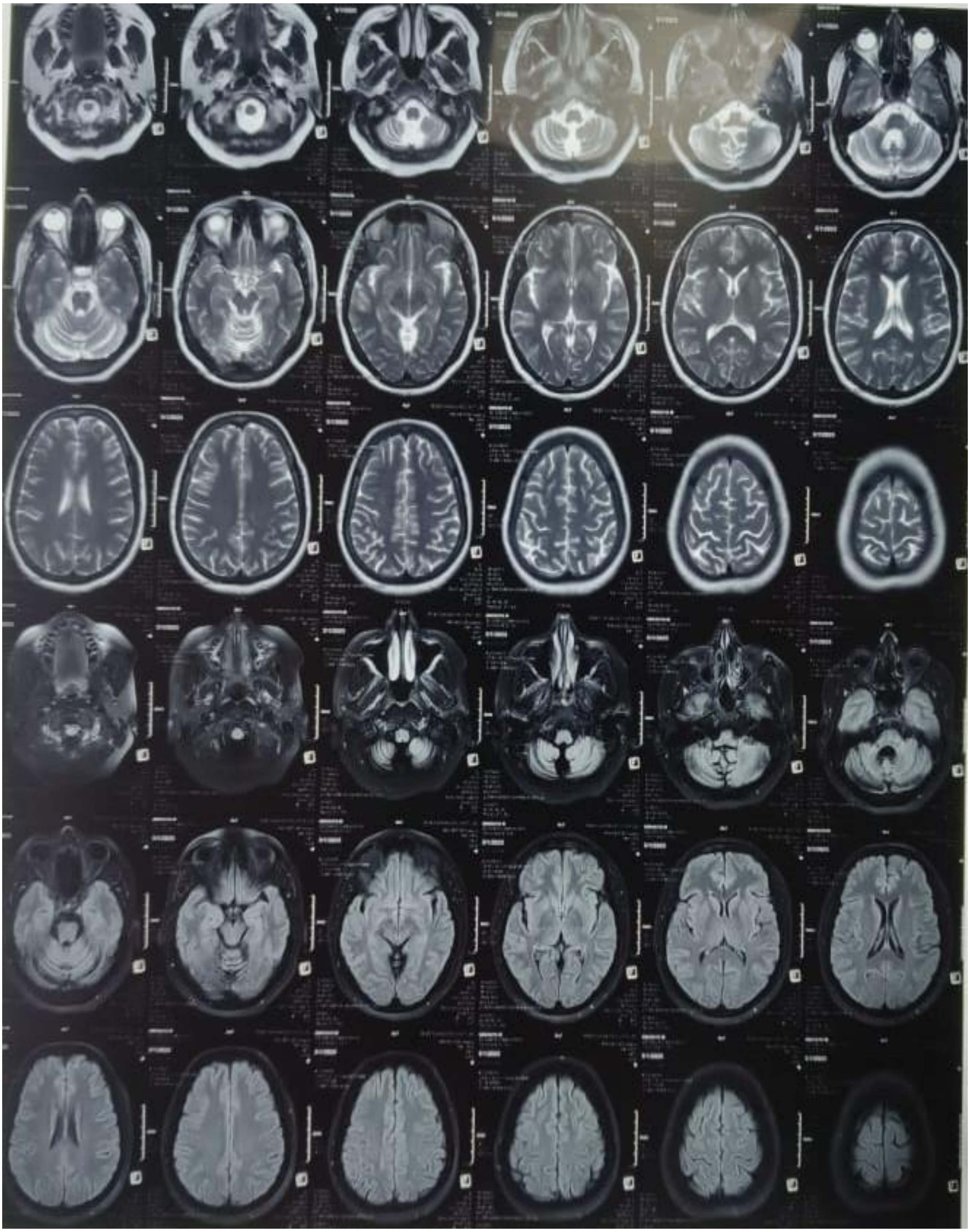

Figure 1: MRI image showing mild cerebellar atrophy.

The whole exome sequencing test identified the heterozygous missense variant "c.206G>C; p.Cys69Ser," detected in the *STUB1* gene on chromosomal position chr16:681198:G>C. This variant is noted to have a total depth of 74X. It is located in exon 2 of the transcript NM_005861.4 and it leads to a change in amino acid from Cysteine to Serine at codon 69 (Table 1). This variant has not been reported in ClinVar and dbSNP databases. This variant has not been reported in population frequency databases such as gnomAD and ExAC. This variant is predicted to be deleterious by in silico prediction tools such as AlphaMissense MutationTaster DANN PrimateAI. Aggregated prediction score for the variant is 0.56 which suggests it to be uncertain. As per ACMG classification, the variant can be classified as Uncertain Significance with criteria PM1, PM2, PM5 and PP2.

Table 1: Sequence variants related to phenotype.

Gene (Transcript)	Location	DNA/Protein Change	Zygosity	Inheritance	Classification	Associated Disease/OMIM
STUB1 (+) NM_005861.4	Exon 2	c.206G>C p.Cys69Ser	Heterozygous	Autosomal Dominant/ Autosomal Recessive	Uncertain Significance	Spinocerebellar ataxia 48 (#618093) Spinocerebellar ataxia, autosomal recessive 16 (#615768)

Discussion

The advent of next-generation sequencing technologies including targeted multigene panels and whole-exome sequencing have markedly advanced the molecular characterization of rare and genetically heterogeneous disorders such as SCAs. These approaches have facilitated the discovery of novel disease-associated genes and expanded both the phenotypic spectrum and inheritance patterns linked to specific loci [12]. For example, mutations in the *STUB1* gene were initially identified as the cause of *SCAR16*, a rare autosomal recessive ataxia characterized by early-onset cerebellar ataxia, cognitive decline, and pronounced cerebellar atrophy, often accompanied by hypogonadotropic hypogonadism, extrapyramidal, or pyramidal features [4,13]. In the revised classification of inherited ataxias, *SCAR16* has been renamed *ATX-STUB1* [14]. Subsequently, a novel autosomal dominant ataxia, SCA48 (MIM# 618093), was reported in a large Spanish family harbouring a heterozygous *c.823_824delCT STUB1* variant. This condition was associated with symptoms of Cerebellar Cognitive Affective Syndrome (CCAS), which in some cases preceded the motor manifestations of cerebellar ataxia [1]. Later studies described additional SCA48 families, further expanding the clinical presentation associated with this gene [15].

Among the various SCA subtypes, SCA1 was the first to be genetically defined, linked to a CAG trinucleotide repeat expansion located within exon 8 of the *ATXN1* gene [16]. The *ATXN1* gene encodes a polyglutamine-containing protein (Ataxin-1 or ATXN1) that localizes to both the cytoplasm and nucleus [17]. Although its complete role in neurodegeneration is yet to be fully understood, *ATXN1* is known to regulate transcription and RNA metabolism [18]. It interacts with various transcriptional and splicing regulators *in-vivo*, including the transcriptional repressor capicua (CIC), mRNA splicing factor RBM17, and other cofactors such as RORa, Tip60, SMRT, LANP, and PQBP-1. Interestingly, *ATXN1*'s RNA-binding capacity is inversely proportional to the length of its polyglutamine tract. Moreover, *ATXN1* undergoes multiple post-translational modifications such as phosphorylation, ubiquitination, sumoylation, and transglutamination that can influence its stability, gene-regulatory activity, and ultimately contribute to SCA1 pathogenesis [19].

Recent studies suggest a genetic interplay between *STUB1* and *ATXN8* expanded alleles, potentially contributing to the pathogenic mechanisms of SCA8 [20]. These findings further underscore the critical role of *STUB1* in maintaining cerebellar integrity and function [21]. In line with these observations, the variant identified in our case "c.206G>C; p.Cys69Ser" in the *STUB1* gene (chromosomal position chr16:681198:G>C) is predicted to result in a cysteine-to-serine substitution at codon 69. This alteration likely accounts for the observed SCA48 phenotype, including subacute-onset ataxia, broad-based gait, mild limb incoordination, and mild dysarthria. To our knowledge, this c.206G>C (p.Cys69Ser) variant of *STUB1* has not been previously reported in Indian patients.

Despite these insights, the precise molecular mechanisms underlying SCA48 pathogenesis remain incompletely defined. The *STUB1* gene encodes the C-terminus of HSC70-interacting protein (CHIP), a multifunctional protein that acts as both an E3 ubiquitin ligase and a molecular cochaperone [22,23]. CHIP comprises three structural domains: (i) An N-terminal tetratricopeptide repeat (TPR) domain that recruits molecular chaperones, (ii) A central helical hairpin region (residues 128–225), and (iii) A C-terminal U-box domain responsible for ubiquitin ligase activity via E2 enzyme recruitment [24]. Previous studies have highlighted CHIP's pivotal role in maintaining protein homeostasis through its E3 ligase activity, where loss or dysfunction can lead to protein misfolding and pathological aggregation [13].

Reports of the *STUB1* mutation causing Spinocerebellar Ataxia type 48 (SCA48) have been documented in Asian populations [25], India is known to have a high prevalence of SCA overall, but the most common types found in the country are SCA2 and SCA12 [26].

In conclusion, though other forms of SCA *viz.* SCA2 and SCA12 have been commonly reported from India, we are reporting an unusual, uncommon, and novel de novo *STUB1* gene variant "c.206G>C; p.Cys69Ser," in the chromosomal position chromosomal position chr16:681198:G>C leading to change in amino acid from Cysteine to Serine at codon 69 could cause SCA48 in a 50-year-old female patient from southern India presented with clinical conditions such as subacute ataxia with broad-based gait, mild incoordination of limbs, and mild dysarthria.

Patient Consent Declaration

Authors hereby declare that they have obtained patient consent.

Conflict of Interest

None

Funding

None to declare.

References

1. Genis D, Ortega-Cubero S, San Nicolás H, Corral J, Gardenyes J, de Jorge L et al. Heterozygous STUB1 mutation causes familial ataxia with cognitive affective syndrome (SCA48). Neurology. 2018;91(21):e1988-e1998.
2. Coarelli G, Coutelier M, Durr A. Autosomal dominant cerebellar ataxias: new genes and progress towards treatments. Lancet Neurol. 2023; 22:735-49.
3. Sullivan R, Yau WY, O'Connor E, Houlden H. Spinocerebellar ataxia: an update. J Neurol. 2019; 266:533-44.
4. Lieto M, Riso V, Galatolo D, De Michele G, Rossi S, Barghigiani M et al. The complex phenotype of spinocerebellar ataxia type 48 in eight unrelated Italian families. Eur J Neurol. 2020;27(3):498-505.
5. Sharma P, Sonakar AK, Tyagi N, Suroliya V, Kumar M, Kutum R et al; GOMED-Ataxia study group. Genetics of Ataxias in Indian Population: A Collative Insight from a Common Genetic Screening Tool. Adv Genet (Hoboken). 2022;3(2):2100078.
6. De Michele G, Galatolo D, Barghigiani M, Dello Iacovo D, Trovato R, Tessa A et al. Spinocerebellar ataxia type 48: last but not least. Neurol Sci 2020a; 41(9):2423-2432.
7. Shi Y, Wang J, Li JD, Ren H, Guan W, He M et al. Identification of CHIP as a novel causative gene for autosomal recessive cerebellar ataxia. PLoS ONE. 2013;8:e81884.
8. Landrum MJ, Lee JM, Benson M, Brown G, Chao C, Chitipiralla S et al. ClinVar: public archive of interpretations of clinically relevant variants. Nucleic Acids Res 2016;44:D862-D868.
9. De Michele G, Salvatore E, Cocozza S, Filla A, Santorelli FM. Of cognition and cerebellum in SCA48. Neurogenetics. 2020b;21(2):145-146.
10. Mengel D, Traschutz A, Reich S, Leyva-Gutiérrez A, Bender F, Hauser S et al. A de novo STUB1 variant associated with an early adult-onset multisystemic ataxia phenotype. J Neurol 2021; 268:3845-3851.
11. Choi S, Park SR, Jang JH, Ahn JH. Spinocerebellar Ataxia 48 Patient with a Novel De Novo Variant of STUB1. J Clin Neurol. 2022;18(6):714-716.
12. Synofzik M, Schule R. Overcoming the divide between ataxias and spastic paraplegias: Shared

phenotypes, genes, and pathways. Mov Disord. 2017; 32:332–345.
13. Shi CH, Schisler JC, Rubel CE, Tan S, Song B, McDonough H et al. Ataxia and hypogonadism caused by the loss of ubiquitin ligase activity of the U box protein CHIP. Hum Mol Genet. 2014;23(4):1013-24.
14. Beaudin M, Matilla-Duenas A, Soong BW, Pedroso JL, Barsottini OG, Mitoma H et al. The Classification of Autosomal Recessive Cerebellar Ataxias: A Consensus Statement from the Society for Research on the Cerebellum and Ataxias Task Force. Cerebellum. 2019;18(6):1098-1125.
15. De Michele G, Lieto M, Galatolo D, Salvatore E, Cocozza S, Barghigiani M et al. Spinocerebellar ataxia 48 presenting with ataxia associated with cognitive, psychiatric, and extrapyramidal features: A report of two Italian families. Parkinsonism Relat Disord. 2019; 65:91-96.
16. Banfi S, Servadio A, Chung MY, Kwiatkowski TJ Jr, McCall AE, Duvick LA et al. Identification and characterization of the gene causing type 1 spinocerebellar ataxia. Nat Genet. 1994;7(4):513-20.
17. Orr HT. Cell biology of spinocerebellar ataxia. J Cell Biol. 2012;197(2):167-77.
18. Matilla-Duenas A, Sánchez I, Corral-Juan M, Dávalos A, Alvarez R, Latorre P. Cellular and molecular pathways triggering neurodegeneration in the spinocerebellar ataxias. Cerebellum. 2010;9(2):148-66.
19. Kumaran D, Hasan G. Spinocerebellar ataxia 1: case and cohort-based studies in India. Curr Sci. 2015;108(5):889–92.
20. Baviera-Munoz R, Carretero-Vilarroig L, Pedro-Ibor A, Jaijo T, Del Valle-Carranza A, Martínez-Torres I et al. STUB1 Mutations as Possible Genetic Modifiers in Spinocerebellar Ataxia Type 8. Mov Disord. 2024;39(9):1641-1644.
21. Li J, Xie W, Chen JM, Xu CZ, Huang YL, Chen S et al. Clinical and functional characterization of a novel STUB1 mutation in a Chinese spinocerebellar ataxia 48 pedigree. Orphanet J Rare Dis. 2024;19(1):471.
22. Qian SB, McDonough H, Boellmann F, Cyr DM, Patterson C. CHIP-mediated stress recovery by sequential ubiquitination of substrates and Hsp70. Nature. 2006;440(7083):551-5.
23. Kalia LV, Kalia SK, Chau H, Lozano AM, Hyman BT, McLean PJ. Ubiquitinylation of α-synuclein by carboxyl terminus Hsp70-interacting protein (CHIP) is regulated by Bcl-2-associated athanogene 5 (BAG5). PLoS One. 2011;6(2):e14695.
24. Umano A, Fang K, Qu Z, Scaglione JB, Altinok S, Treadway CJ et al. The molecular basis of spinocerebellar ataxia type 48 caused by a de novo mutation in the ubiquitin ligase CHIP. J Biol Chem. 2022; 298:101899.
25. van Prooije T, Ibrahim NM, Azmin S, van de Warrenburg B. Spinocerebellar ataxias in Asia: Prevalence, phenotypes and management. Parkinsonism Relat Disord. 2021; 92:112-118.
26. Faruq M, Shakya S, Garg A, Srivastava AK. Spinocerebellar Ataxia 2 and 12 Mutations in an Indian Family with Cerebellar Ataxia and Slow Saccades. Mov Disord Clin Pract. 2014;1(3):267-270.