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A New Missense Mutation of SPTBN2 with Spinocerebellar Ataxia Type5: A Case Report

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1. Abstract

Background: Spinocerebellar ataxia type 5 (SCA5), dominant spinocerebellar ataxia caused by mutations in the SPTBN2 gene, SCA5 is clinically described as a slowly progressive cere- bellar ataxia with little involvement of the brainstem or spinocere-bellar tract or brain, occurring mainly in adulthood.

Case report: A 31-year-old female patient presented with progressive hearing loss for 12 years, walking instability for one year, dysphagia and dysarthria for more than four months, with the tremor in the tongue muscle and numbness below both knees. Brain MRI suggested demyelinating changes in bilateral Hemi-ov- al centers. A heterozygous mutation of the SPTBN2 gene in exon 16 of chromosome 11 was detected in peripheral blood DNA (c 3124G>C).

Discussion: A novel missense mutation c 3124G>C,p (Glu1024Gln) was detected in peripheral blood DNA, which maybe related to SCA5 as assessed by patient characteristics and re- lated examinations, a missense mutation has not been reported by the HGMD database, ESP6500siv2_ ALL, the 1,000-person genome(1000g2015aug_ALL), and the dbSNP147 database, no studies have been published to determine the potential for patho- genicity. Bioinformatics software predicts the possibility of path- ogenicity at this site, so the diagnosis needs further study. A com- plete whole-exon genetic examination of V4 revealed a heterozy- gous mutation in the GRHL gene on chromosome 8 (c285-10C>T) (splicing) and a heterozygous mutation in exon 70 of the MYO1A gene on chromosome 12 (c1332 3G>A)(splicing). However, ac-

cording to ACMG guidelines, the clinical significance of the mutation was unknown, no association was reported in the clinical database, and no pathogenicity analysis of this locus was found in theClin Var database. Therefore, it is considered that hearing loss may be related to genetic variation, but the pathogenicity is unknown. Simultaneous M002: mitochondrial loop gene full-length panel (capture) suggested an MT-TA gene mutation chrM-5628(T>C), which was previously reported as a suspected pathogenic variant.

2. Introduction

Spinocerebellar ataxia is a heterotypic neurodegenerative disease characterized by progressive cerebellar ataxia, dysarthria, dyspha- gia, and nystagmus [1]. SCA5 type (SCA5) is the dominant type associated with SPTBN2 mutations [2], clinically described as limb and gait ataxia (90%), but trunk ataxia, sensory deficits, eye movement abnormalities, dysarthria, and hyperactive deep tendonreflexes are also prevalent (25-90%) [3]. Patients often have dif- ficulty in performing fine motor coordination, but rarely require a wheelchair until late in the course of the disease. The onset usually occurs in the early 30 years of age, but it ranges from infancy to 68years of age [4]. The Spectrin nonerythrocytic 2 gene (SPTBN2) encoding β-III spectrin is considered to be the causative gene of SCA5 [4-8], a 2390-amino acid calponin homology (CH) domain including the N-terminus, 17 repeat sequences and the C- termi- nus prick homology (PH) domain [5]. Beta-III spectrin is a protein that functions in membrane structure and transport, involved in neurotransmitter transporters and ion channel anchoring [4,9]. It is mainly expressed in the central nervous system, with the highest

content in Purkinje cells [6]. Loss of β-III spectrin function can lead to cerebellar dysfunction and degeneration, resulting in thinning of dendrites, excessive protrusion of dendrites, reduction of sodium current, and abnormal neurotransmission of glutamate [9].

3. Case Report

The proband was a 31-year-old woman who had hearing loss in both ears from the age of 19 years and was not given attention at that time. In the past year, she had unstable walking, easy falling, difficulty standing with eyes closed, aggravated with hoarseness for four months, dysphagia, drinking cough, no eating cough, self-conscious numbness below both knees, no headache, dizziness, blurred vision, and other discomforts. On June 29, 2020, the patient visited the Xijing Hospital of the Fourth Military Medical University. The complete otorhinolaryngology showed that the tympanic membrane was intact and slightly cloudy; lymphoid tissue hyperplasia at the base of the tongue, with slight hyperemia in both vocal cords. Axial plain scan of the temporal bone: the left jugular bulb is high, and no special diagnosis and treatment was given. On August 27, 2020, she went to the outpatient clinic of the General Hospital of Ningxia Medical University. The Department of Neurology was admitted to the hospital as "the cause of ataxia to be investigated".

Physical examination revealed the patient was conscious, had dysarthria, decreased gross hearing in both ears, slightly weakened bilateral biceps reflex, triceps reflex, radial periosteal reflex, active bilateral knee reflex, and weakened ankle reflex. The bilateral finger-nose test was not stable and accurate, the bilateral rotation test was coordinated, and the bilateral heel-knee-shin test was stable and accurate. Eyes closed difficult to establish positive signs. Ataxia gait.

Auxiliary examination showed electromyography (sleeve): multiple peripheral nerve damage (both motor and sensory nerves were involved); EMG: neurogenic damage of both lower extremities (involving L4-5, S1 segmental ramus muscles). Cervical vertebral MRI plain scan: cervical vertebral arch, instability, cervical vertebral body hyperplasia and degeneration; cervical 5-6 intervertebral disc herniation (central type), dural sac compression at the same level, thickening of ligamentum flavum (Figure 4).

Brain MRI: bilateral lateral ventricle and center semiovale demyelination（Figure 4 and Figure 3）; visual evoked potential (VEP): binocular VEP visual conduction pathway is normal. Somatosensory evoked potentials: Abnormal SEP in both upper extremities (peripheral to deep cortical sensory conduction disturbance); bilateral lower extremity SEP abnormal (peripheral to deep cortical sensory conduction disturbance). According to the clinical characteristics of patients, it is considered that it may be related to hereditary diseases, so it is recommended to improve genetic testing. The patient indicated that he knew and agreed, and the patient's venous blood was drawn and sent to Ningxia Jinyu Medical Laboratory for detection of the subject's sample using fragment analysis technology, Unraveling suggests missense mutation in SPTBN2 (c 3124G>C)(p Glu 1042Gln). (Figure 2). Go to Xijing Hospital of Fourth Military Medical University by yourself to complete the whole exon genetic examination. V4 indicates a heterozygous mutation of the GRHL gene on chromosome 8 (c285-10C>T) (splicing), and a heterozygous mutation in exon 70 of the MYO1A gene on chromosome 12 (c1332 3G>A) (splicing). At the same time, line M002: the full-length panel of mitochondrial ring gene (captured) indicates the mutation of MT-TA gene (4817T>C), and the mutation site is chrM-5628.

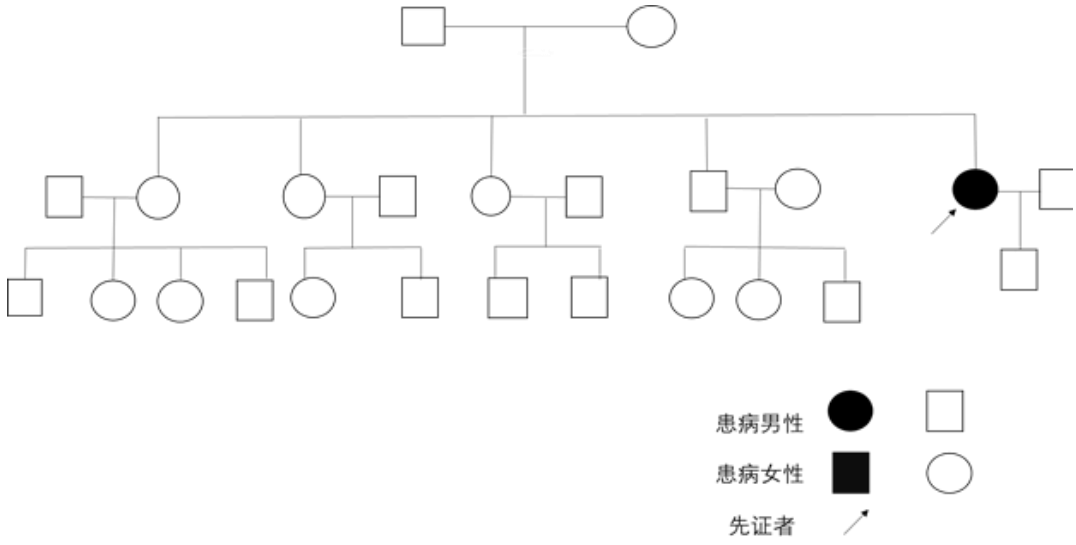


Figure 1: This is the pedigree of the patient. The patient suffered hearing loss, walking instability, dysphagia, and dysarthria, with the tremor of the tongue muscle and numbness below both knee.

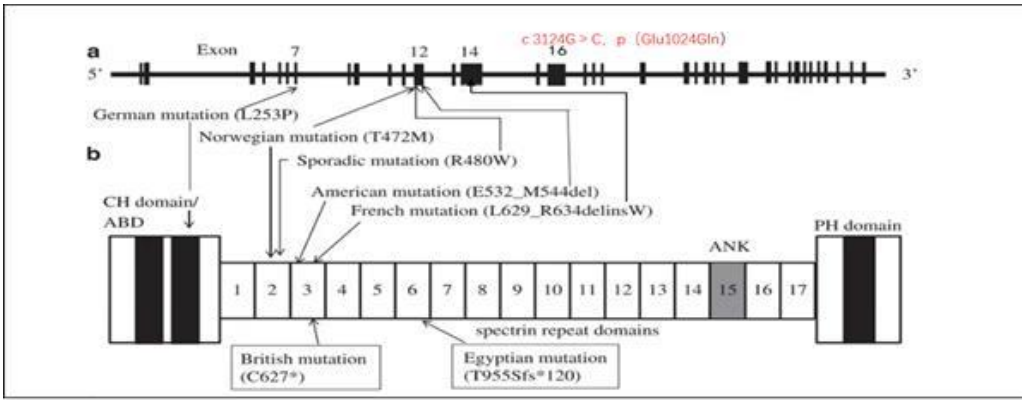


Figure 2: (a) Illustration of exons (filled rectangles) in the SPTBN2 gene. The patient mutation form locates in Exon 16. (b) A schematic representation of the functional domains of β-3 spectrin, modified from the reported representation, [6]is shown along with the positions of all found mutations, exhibiting dominant (upper) or recessive (lower) transmission, so far. CH, calponin homology domain; ABD, actin-binding domain; ANK, ankyrin-binding domain; PH, pleckstrin homology domain.[7]

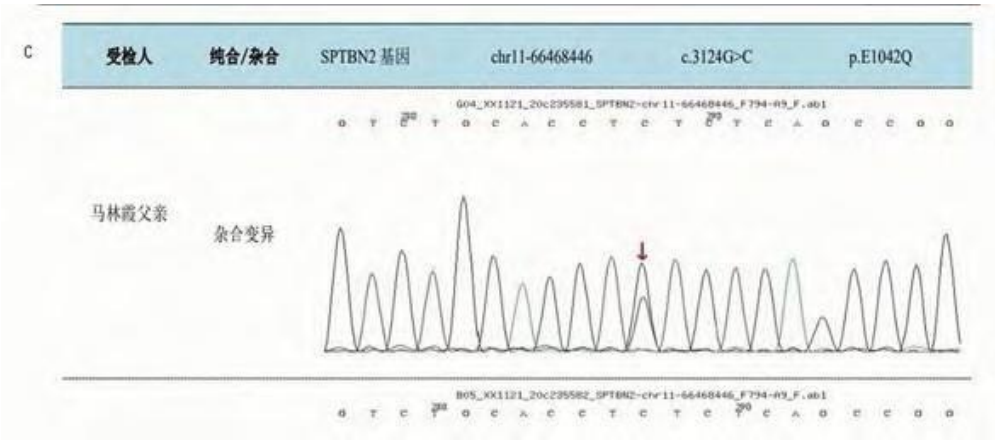
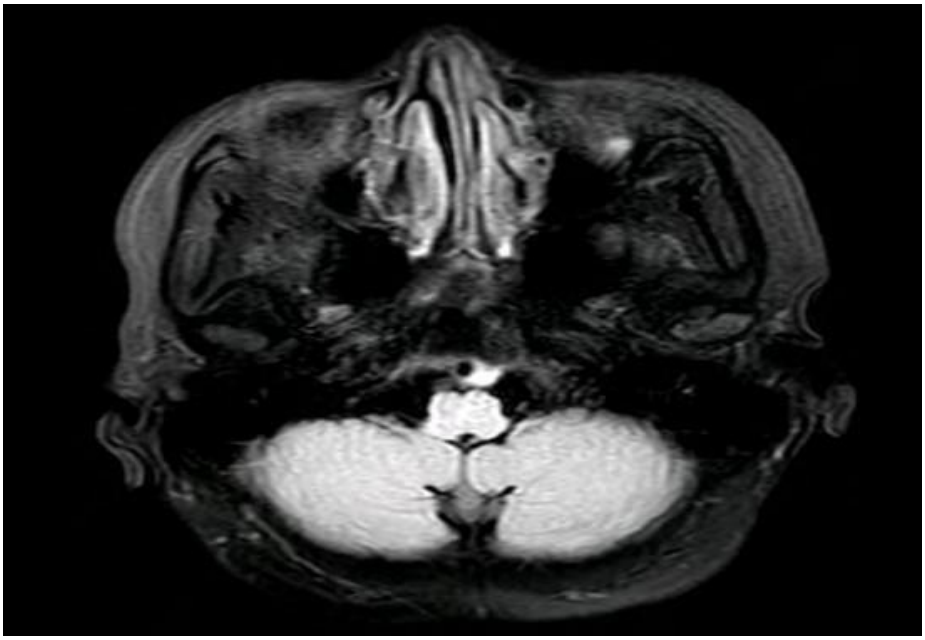


Figure 3: (c) This is a plot of the father's mutation, and the patient has the same mutation



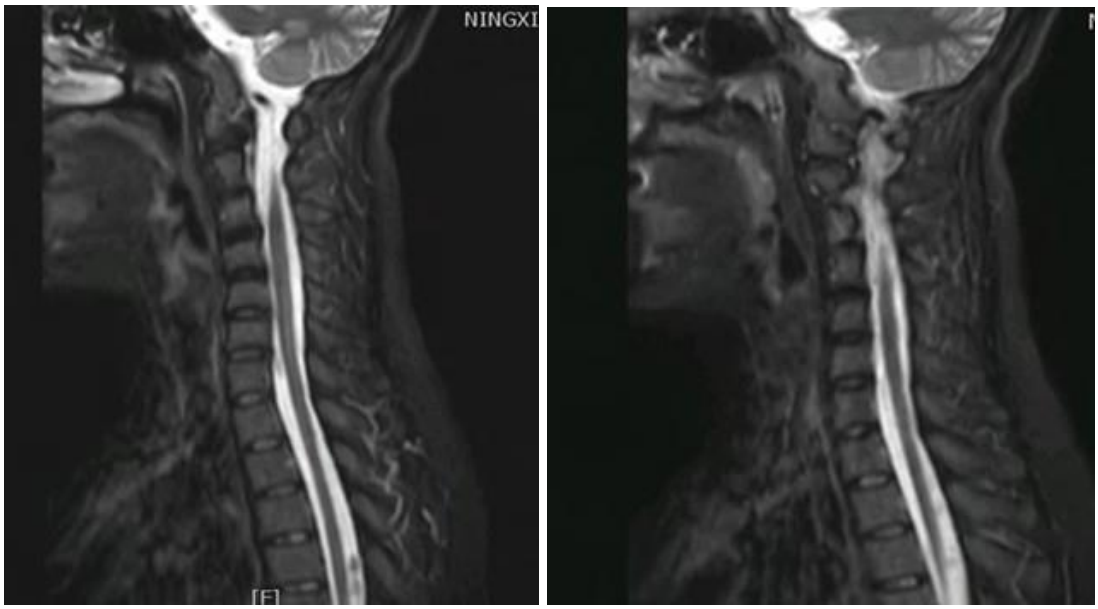


Figure 4: Brain MRI of a patient with SCA5 suggested demyelinating changes in bilateral Hemi-oval centers. (**d**-T2weighted), Cervical (MRI) showed cervical reverse arch, instability, cervical vertebral hyperplasia, and degeneration; cervical 5-6 disc herniation (central type), compression of the same level dural sac, thickening of the ligamentum flavum（**e**-T2weighted）

4. Discussion

In 1994, Ranum and colleagues mapped the disease locus to the centromere region of chromosome 11 [3] and reported the SCA5 family for the first time. The two main branches of this extended family, 56 affected in 10 generations, were descendants of the grandparents of President Abraham Lincoln. Subsequently, in the German national line [10], a shortened syntactic on chromosome 11q13 was found. A slowly progressive cerebellar syndrome is associated with chromosomal regions in a French SCA5 family [11]. SPTBN2 is highly expressed in Purkinje cells, where β-III spectrin is thought to bind proteins to certain plasma membrane domains and thereby maintain membrane protein stability by stabilizing the glutamate transporter EAAT4 and β-III spectrin interactions with the C-terminal domain of the glutamate receptor EAAT4 to stabilize and regulate glutamate uptake in the cell membrane. [5] The mutant form failed to stabilize EAAT4, affecting glutamate signaling in the plasma membrane [6]. The patient presented with unstable walking, dysphagia, dysarthria, tremor of the tongue, and numbness below the knee joint. It was suggested to improve the venous blood DNA test for patients and their families. Fragment analysis revealed a heterozygous mutation of the SPTBN2 gene on chromosome 11 c 3124G>C,p(Glu1024Gln). The father gene test showed a heterozygous mutation, (Figure 2) and the mutation site was normal in the mother gene test. One sister and one little sister of the patient showed heterozygous mutation of the SPTBN gene, and the mutation site was consistent with the mutation site of the patient. However, none of them had clinical manifestations, (Figure 1), and None of his family members had a brain MRI for financial reasons.

The patient attended the Fourth Military Medical University and completed the genetic testing. The whole-exon genetic examination using high-throughput sequencing showed heterozygous mutation (c285-10C>T)(splicing) of GRHL gene on chromosome 8 and heterozygous mutation (c1332 3G>A)(splicing) of exon 70 of MYO1A on chromosome 12. However, according to ACMG guidelines [11], the clinical significance of the mutation was unknown, no association was reported in the clinical database, and no pathogenicity analysis of this locus was found in the Clin Var database. Therefore, it is considered that hearing loss may be related to genetic variation, but the pathogenicity is unknown (grainyhead-like2 ,GRHL2). The gene is associated with autosomal sensorineural hearing loss and affects the DFNA28 locus [13]. Studies have also shown that it is associated with age-related hearing loss [14]. This gene encodes the GRHL2 protein, which is highly expressed in epithelial cells within the cochlear duct and plays a key role not only in embryonic development but also in maintaining epithelial cell function throughout the life cycle. Mutations in this gene are associated with hearing loss in humans. As a transcriptional activator, GRHL2 regulates the expression of apical connexin and desmosine. Using zebrafish transposon-mediated gene capture, GRHL2 was found to regulate the development of intercellular junctions in the inner ear, maintaining the composition and concentration of the inner ear cavity. To provide the necessary environment for the normal development of the otolith and semicircular system, and to ensure the functionality of the hearing and balance system [15]. Therefore, it is thought that hearing loss may be related to genetic variation, but its pathogenicity is unknown. Patients also performed M002: mitochondrial loop gene full-length panel by high-throughput sequencing (capture) suggesting an MT-TA gene mutation chrM-5628(T>C), which has been previously

reported as a suspected pathogenic variant. This mutation may present late-onset chronic progressive external ophthalmoplegia, sensorineural deafness, dysphagia, and mild proximal myopathy, as well as mitochondrial metabolic disorders such as ischemic cardiomyopathy, type 2 diabetes, and hyperlactatemia [16].

5. Conclusion

the patient presented with walking instability, dysphagia, dysarthria, tongue muscle tremor, numbness below both knees, and loss of hearing in both ears during her 30s. A new missense mutation c 3124G>C,p(Glu1024Gln) was detected in peripheral blood DNA. The mutation is located in the repeat of the spectrin area. HGMD database, ESP6500siv2_ALL, 1000g 2015aug_ALL, and dbSNP147 databases have not been reported. Bioinformatics software predicts the possibility of pathogenicity, which is considered highly likely, but the diagnosis needs further study. Other clinical features of the patient may be related to GRHL2 and MT-TA gene mutations, which may be suspected pathogenic variants reported in previous literature, and further study is needed to confirm the diagnosis.

6. Conflict of Interest Statement

All the authors declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

7. Publication Ethics

The ethics were approved by the General Hospital of Ningxia Medical University Research Ethics Committee [KYLL-2021-436]. And First-Class Discipline Construction Founded Project of NingXia Medical University and the School of Clinical Medicine, the number is NXYLXK2017A05.

8. Consent for Participation and Publication

All the cases and controls signed the informed consent before we collected their blood, and the informed consent for the child was signed by their parents on their behalf (under the age of eighteen).

References

1. Rossi M, Perez-Lloret S, Doldan L. Autosomal dominant cerebellar ataxias: a systematic review of clinical features. Eur J Neurol. 2014; 21(4): 607-615.
2. Rosini F, Pretegiani E, Battisti C, Dotti MT, Federico A, Rufa A, et al. Eye movement changes in autosomal dominant spinocerebellar ataxias. Neurol Sci. 2020; 41(7): 1719-1734.
3. Ranum LP, Schut LJ, Lundgren JK, Orr HT, Livingston DM. Spinocerebellar ataxia type 5 in a family descended from the grandparents of President Lincoln maps to chromosome 11. Nat Genet. 1994; 8(3): 280-284.
4. Liu LZ, Ren M, Li M. A Novel Missense Mutation in the Spectrin Beta Nonerythrocytic 2 Gene Likely Associated with Spinocerebellar Ataxia Type 5. Chin Med J (Engl). 2016; 129(20) :2516-2517.
5. Jackson M, Song W, Liu MY. Modulation of the neuronal glutamate transporter EAAT4 by two interacting proteins. Nature. 2001; 410(6824): 89-93.
6. Ikeda Y, Dick KA, Weatherspoon MR. Spectrin mutations cause spinocerebellar ataxia type 5. Nat Genet. 2006; 38(2): 184-190.
7. Wang Y, Koh K, Miwa M, Yamashiro N, Shindo K, Takiyama Y, et al. A Japanese SCA5 family with a novel three-nucleotide in-frame deletion mutation in the SPTBN2 gene: a clinical and genetic study. J Hum Genet. 2014; 59(10): 569-573.
8. Cho E, Fogel BL. A family with spinocerebellar ataxia type 5 found to have a novel missense mutation within a SPTBN2 spectrin repeat. Cerebellum. 2013; 12(2): 162-164.
9. Perkins E, Suminaite D, Jackson M. Cerebellar ataxias: β-III spectrin's interactions suggest common pathogenic pathways. J Physiol. 2016; 594(16): 4661-4676.
10. Bürk K, Zühlke C, König IR. Spinocerebellar ataxia type 5: clinical and molecular genetic features of a German kindred. Neurology. 2004; 62(2): 327-329.
11. Stevanin G, Herman A, Brice A, Dürr A. Clinical and MRI findings in spinocerebellar ataxia type 5. Neurology. 1999; 53(6): 1355-1357.
12. Qiuju W, Yiping S, Lingqian W, Shaoke C, Zijiang C, Songbin F, et al. Classification criteria and guidelines for genetic variation [J]. Science in China: Life Sciences. 2017; 47(06).
13. Peters LM, Anderson DW, Griffith AJ. Mutation of a transcription factor, TFCP2L3, causes progressive autosomal dominant hearing loss, DFNA28. Hum Mol Genet. 2002; 11(23): 2877-2885.
14. Van Laer L, Van Eyken E, Fransen E. The grainyhead like 2 gene (GRHL2), alias TFCP2L3, is associated with age-related hearing impairment. Hum Mol Genet. 2008; 17(2): 159-169.
15. Han Y, Mu Y, Li X. Grhl2 deficiency impairs otic development and hearing ability in a zebrafish model of the progressive dominant hearing loss DFNA28. Hum Mol Genet. 2011; 20(16): 3213-3226.
16. Toncheva D, Serbezov D, Karachanak-Yankova S, Nesheva D. Ancient mitochondrial DNA pathogenic variants putatively associated with mitochondrial disease. PLoS One. 2020; 15(9): e0233666.