



SPTBN2와 연관된 spinocerebellar ataxia type 5를 진단받은 환자

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A Patient Diagnosed with Spinocerebellar Ataxia Type 5 associated with SPTBN2: Case Report

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Spinocerebellar ataxias (SCAs) are autosomal dominant neurodegenerative disorders which disrupt the afferent and efferent pathways of the cerebellum that cause cerebellar ataxia. Spectrin beta non-erythrocytic 2 (*SPTBN2*) gene encodes the β -III spectrin protein with high expression in Purkinje cells that is involved in excitatory glutamate signaling through stabilization of the glutamate transporter, and its mutation is known to cause spinocerebellar ataxia type 5. Three years and 5 months old boy with delayed development showed leukodystrophy and cerebellar atrophy in brain magnetic resonance imaging (MRI). Diagnostic exome sequencing revealed that the patient has heterozygous mutation in *SPTBN2* (p.Glu1251Gln) which is a causative genetic mutation for spinocerebellar ataxia type 5. With the patient's clinical findings, it seems reasonable to conclude that p.Glu1251Gln mutation of *SPTBN2* gene caused spinocerebellar ataxia type 5 in this patient.

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Introduction

Spinocerebellar ataxias (SCAs) are a clinically heterogeneous group of autosomal dominant neurodegenerative disorders that cause cerebellar ataxia by disrupting the afferent and efferent pathways of the cerebellum¹. The typical age of onset is between the 30s and 40s, and presentation can be with different clinical symptoms. Consequently, more than 30 types of SCA have been described so far². There are three major classes of SCA. A first category includes SCA caused by CAG repeat expansions. A second category contains the SCA which are due to repeat expansions of the respective disease genes. A third category is SCA caused by conventional mutations in specific genes like missense and deletions. SCA5 belongs to third category of SCAs³.

In 2006, heterozygous mutations in the spectrin beta non-erythrocytic 2 gene (*SPTBN2*), which encodes β -III spectrin, were found to cause spinocerebellar ataxia type 5 (SCA5)⁴. The expression of *SPTBN2* is particularly high in the Purkinje cells involved in excitatory glutamate signaling through stabilization of the glutamate transporter. SCA5 has a prevalence of <1% and is a rare cause of

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ataxia⁵). Although SCA5 is characterized by pure cerebellar symptoms, with over 90% of affected individuals primarily exhibiting limb and gait ataxia, other features may occur⁶. Indeed, dysarthria, sensory deficits, truncal ataxia, abnormal eye movements, and hyperactive deep tendon reflexes are present in 25%–90% of patients⁷. In this case report, we present the details of a male patient diagnosed with SCA5 caused by a novel heterozygous mutation in *SPTBN2* (p.Glu1251Gln).

Case report

The patient was three years and 5 months old when he was brought to our clinic with the chief complaint of developmental delay. The patient's height was 91 cm (50–75 percentile) and weighted 14 kg (50–75 percentile) without dysmorphism when he visited our clinic. He was born by cesarean section at gestational age of 39 weeks, weighing 2.98 kg, and his perinatal history was unremarkable. Also he had no specific family history. Patient's parents had genetic test which showed no genetic mutation. An investigation of his developmental history revealed that he gained control over his head movements at 3 months and could roll over at 4–5 months of age. His parents noticed motor developmental delay at the age by which he should have learnt to stand/walk. When we had physical examination, he did not show pyramidal sign or extrapyramidal sign. His muscle tone in proximal part was hypotonic. He eventually stood up at 15 months and started walking 20 months of age. Also we have done eye examination which showed normal. To evaluate delayed development, he was tested using the Bayley developmental scale, and the results revealed that he

had mental development equivalent to that of a 20-month-old child and motor development equivalent to that of a 15-month-old child. Both results were below the 0.1 percentile for his age group. At the most recent assessment, he could walk independently, but did so with an unstable wide-based gait. He could talk three to four words sentences. Results of chromosome analysis, metabolic work-up, genetic study for proteolipid protein 1, and other general laboratory examinations performed at other hospitals were normal. However, leukodystrophy and mild cerebellar atrophy were identified on a brain magnetic resonance imaging (MRI) scan, performed one year before visiting our clinic, and when we repeated the MRI scan, we noted progression of the leukodystrophy but no change in the mild cerebellar atrophy (Fig. 1). Based on the lack of a clear clinical diagnosis and our suspicion of an underlying genetic disorder due to delayed development, gait disturbance, and cerebellar atrophy in brain MRI, diagnostic whole exome sequencing was performed.

The result revealed a novel heterozygous mutation in *SPTBN2* (p.Glu1251Gln), which was considered compatible with the causative mutation in SCA5 (Fig. 2). Sanger sequencing was performed to confirm the genetic disorder. At present, the patient is undergoing regular physical therapy and treatment with dantrolene, which have improved the muscle spasticity in his legs.

Discussion

In this report, we have presented a case of SCA associated with a mutation in the *SPTBN2* gene. SCA5 is a human neurode-

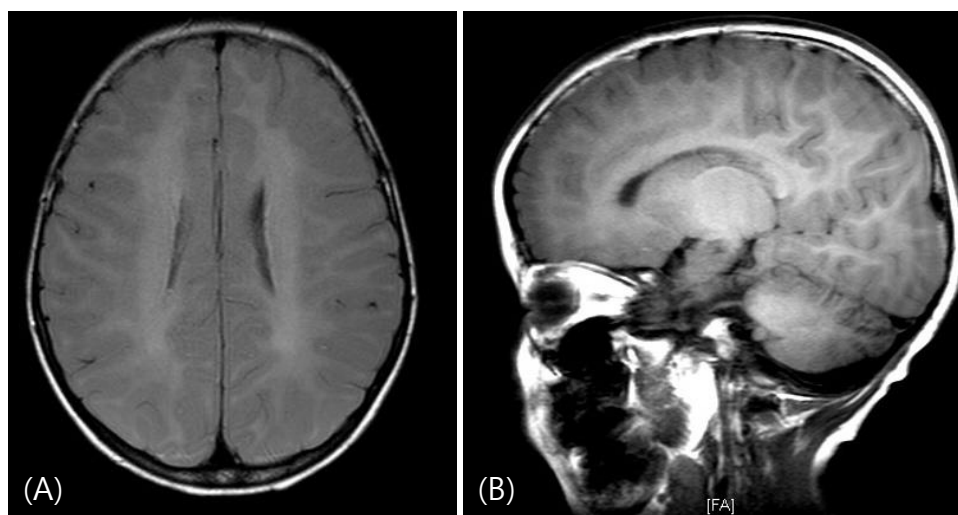


Fig. 1. (A) The bilateral symmetrical diffuse T2 high signal intensity at the cerebral white matters, including both subcortical U-fibers and periventricular white matter (T2 FLAIR axial image), (B) mild cerebellar atrophy.

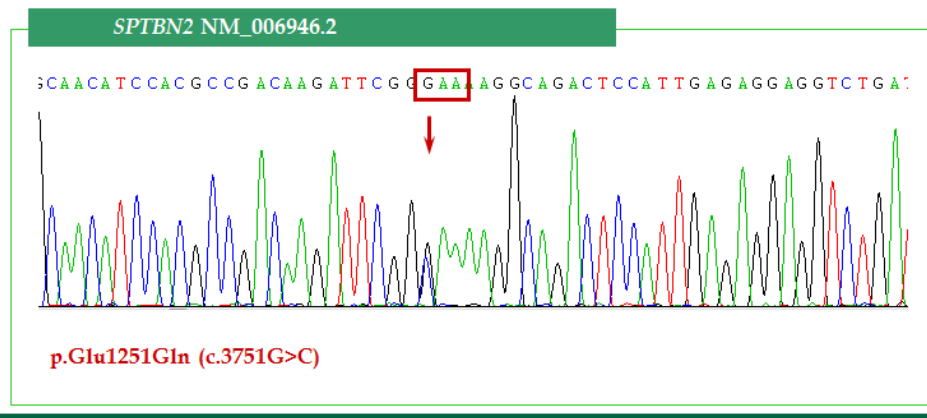


Fig. 2. Sanger sequencing showing p.Glu1251Gln mutation.

generative disorder that causes gait ataxia, slurred speech, vision abnormalities, and loss of coordinated movement of the extremities⁶. In some cases, patients can develop pyramidal or extrapyramidal signs, ophthalmoplegia, or cognitive impairment¹¹. However, the typical age of onset is between the 30s and 40s, with the disease restricted to neurodegeneration of the cerebellum. SCA5 has a variable age of onset and slow disease progression. Childhood onset is associated with a more severe course, purely cerebellar clinical features, predominant Purkinje cell loss, and global cerebellar atrophy. In this case, onset age is young which lead to more severe course, but active rehabilitation can minimize functional loss in patient. Therefore, unknown cerebellar ataxia or cerebellar atrophy should consider diagnostic whole exome sequencing irrespective of onset age.

SCA5 is an autosomal dominant disease caused by mutations in the *SPTBN2* gene that encodes β -III spectrin. The highest expression of β -III spectrin is in the Purkinje cells of the cerebellum⁸. At the surface of the plasma membrane in Purkinje cells, *SPTBN2* stabilizes Excitatory Amino Acid Transporter 4 (EAAT4)¹¹. Although it is known that the product of the mutant gene fails to stabilize EAAT4 at the plasma membrane, which adversely affects the glutamate signaling pathway⁹, it is still unclear how mutations in β -III-spectrin cause Purkinje cell death in patients with SCA5. Some evidence has led to the proposal that SCA5 results from the destabilization of specialized synaptic membrane domains or defects in intracellular transport¹⁰. Another possible pathogenic mechanisms of SCA5-associated mutations include transcriptional dysregulation and impaired protein degradation.

In the present case, the patient had significant developmental delay and gait disturbance. However, symptoms can lead to considerable functional declines in physical and social activities. Given that the disease will progress throughout the life, further

assessment is indispensable. Following the patient's progression would facilitate the initiation of symptom-targeting therapies, including medication, physical therapy, and rehabilitation, as required to minimize functional loss.

This patient presented with delayed development and gait disturbance, and an MRI scan of his brain revealed cerebellar atrophy and progressive leukodystrophy. Whole exome sequencing revealed a missense mutation (p.Glu1251Gln) in the *SPTBN2* gene on chromosome 11. Three mutations in this gene are known to cause SCA5; these comprise one missense mutation that interferes with the actin binding site in the second calponin homology domain (p.L253P) and 2 deletions (p.E532_M544del and p.L629_R634delinsW) within the third SPEC domain of the protein that are believed to disrupt the triple alpha-helical structure of the repeats⁷. Although there are no previous reports of the p.Glu1251Gln mutation causing SCA5, given this patient's clinical findings, it is reasonable to conclude that it was causative in this case.

In conclusion, cerebellar dysfunction is the primary characteristic of SCA, but it can also be associated with various other clinical features. Brain MRI scanning is essential in identifying cerebellar atrophy, while diagnostic whole exome sequencing can be helpful in diagnosis with typical symptoms when other causes of cerebellar ataxia cannot be ruled out. Further genetic studies are required to clarify the role of the identified genes in SCA

요약

척추소뇌실조는 임상적으로 다양하게 나타나는 보통염색체 우성 신경변성 (혹은 퇴행성) 질환군으로서, 소녀의 들과 날의 경로를 분열시켜 소녀 실조를 일으키는 것으로 알려져 있다. 전형적인 임상증상

은 30에서 40대에 발현되기 시작하고, 보행실조, 불분명 발음, 시력 이상, 사지의 조화운동 불능, 안구 움직임 제한, 인지 장애 등 다양한 증상의 조합을 특징으로 한다. 본 증례의 환자에서는 exome sequencing을 통하여 SPTBN2 (p.Glu1251Gln)의 새로운 이형접합 돌연변이를 발견하였으며 이것이 SCA5의 원인으로 밝혀졌다. 증례의 환자는 3년 5개월 때 발달지연을 주소로 본원에 내원하였다. 발달지연을 평가하기 위해 베일리 발달 검사에서 모든 영역에서 현저한 지연이 확인되었다. 본원 내원 1년 전 시행한 뇌자기공명영상에서 백색질 형성장애와 약간의 소뇌 위축이 보였다. 잠재적인 유전질환을 의심하여 진단 목적으로 전체엑솜염기서열분석을 시행하였고 결과적으로 SPTBN2의 새로운 이형접합 돌연변이 (p.Glu1251Gln)가 SCA5의 원인 돌연변이로 사료된다. 척수소뇌실조에서 유전자의 역할을 명확하게 규명하기 위해서는 전체엑솜염기서열 분석을 포함한 다양한 방법을 통한 유전자 연구가 필요할 것으로 사료된다.

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