# Spinocerebellar Ataxia-21 in a Turkish Child

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## Abstract

Hereditary cerebellar ataxias are genetically heterogeneous disorders. Autosomal recessive spinocerebellar ataxia-21 (SCAR21) is a neurologic disorder characterized by the onset of cerebellar ataxia, recurrent episodes of liver failure, peripheral neuropathy, and learning disabilities. Herein, we reported a case presented with gait and balance problems, swallowing difficulties, mild delayed motor development, and mild learning disability with SCAR21 that confirmed by mutation analysis in a Turkish child. To the best of our knowledge, this is the first case of SCAR21 from Turkey.

**Keywords:** Ataxia, child, genetic mutation

## Introduction

Hereditary ataxia is a heterogeneous disorder characterized by progressive ataxia combined with/without peripheral neuropathy, extrapyramidal and pyramidal symptoms, seizure, and multiple system involvements.[1] Spinocerebellar ataxia-21 (SCAR21) is characterized by cerebellar ataxia, recurrent episodes of liver failure, chronic liver fibrosis, peripheral neuropathy, and learning disabilities.[2]

In the literature, a few cases have been reported. Here, we report a boy, who presented with recurrent episodes of acute liver failure in early infancy and is affected by cerebellar atrophy, ataxia, peripheral neuropathy (PNP), mild delayed motor development, and mild learning disability. To the best of our knowledge, this is the first case of SCAR21 from Turkey.

## Case Report

A 10-year-old boy was admitted to our hospital because of gait and balance problems, swallowing difficulties, mild delayed motor development, and mild learning disability. His first admission to the hospital was at 9-months of age with unexplanied episode of liver failure triggered by fever. Then, he had a history of a few hospitalizations due to fever of unknown origin, episode of liver failure, and gait disturbance in early childhood in another hospital. His parents told that he was complaining of gradually increasing ataxia and dysarthric speech since the early childhood. In addition, the patient was treated for hypothyroidism when he was 1 year old in another hospital. The parents were consanguineous.

On examination, he had marked cerebellar ataxia with dysmetria on bilateral finger-to-nose and heel-to-knee tests, truncal titubation, dysarthria, and vertical gaze palsy on eye movement with hyperreflexia and pathological reflexes such as extensor plantar responses. Muscle atrophy and weakness were not observed. Fundoscopy showed bilateral peripapillary atrophy. The remainder of the neurological and physical examinations did not reveal abnormalities.

Results of full blood count, serum chemistry, lipid profile, thyroid function tests, serum Vitamin E and B12 levels, alpha-fetoprotein, ceruloplasmin, serum lactate, ammonia, blood and urine amino acids, urine organic acids, and lysosomal enzyme analysis, electrocardiogram, and gene analysis for Friedreich ataxia were all normal. Cerebral magnetic resonance imaging showed cerebellar atrophy [Figure 1]. Nerve conduction studies showed axonal neuropathy.

In this patient and his parents, whole-exome sequencing analysis was performed. Novel homozygous mutation SCYL1:C. 1420C>T was identified in exon 11 of the SCYL1 gene. The mutation was also detected in both parents in heterozygous

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state. We thought that the patient was SCAR21 due to clinical and genetic evaluation.

## Discussion

Autosomal recessive variants in the SCYL1 gene are known to cause SCAR21 and are characterized by mildly delayed motor development and mild intellectual disability, cerebellar ataxia, tremor, hyperreflexia, and cerebellar atrophy. Affected individuals also have recurrent episodes of liver failure in the first decade, resulting in chronic liver fibrosis, as well as later onset of a peripheral neuropathy.[2]

SCAR21 is caused by compound heterozygous mutation in the SCYL1 gene on chromosome 11q13.[2] SCYL1 is highly conserved among eukaryotes and belongs to the SCYL1-like family of catalytically inactive protein kinases, harboring an N-terminal serine-threonine kinase-like domain, a centrally located HEAT repeat domain, and C-terminal protein-interaction motifs. Recent findings by others have demonstrated that SCYL1 represents an important protein at the interface between the Golgi apparatus and the membrane trafficking machinery mediated by coatomer (COPI)-coated vesicles and is likely involved in intracellular transport processes.[3,4]

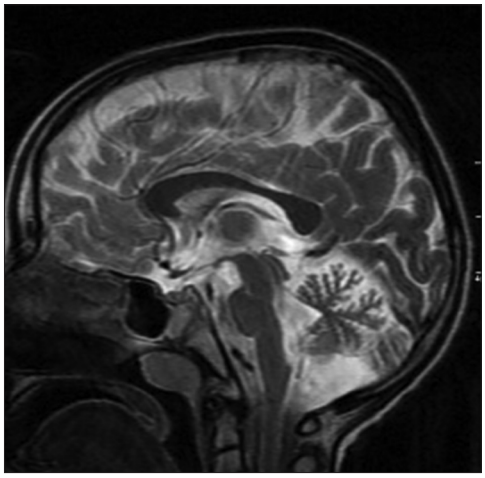

**Figure 1:** Cerebral magnetic resonance imaging showed cerebellar atrophy

The transmission pattern of SCAR21 with hepatopathy in the families reported by Schmidt *et al.* was consistent with autosomal recessive inheritance.[2] They identified compound heterozygous truncating mutations in the SCYL1 gene in 3 patients from 2 unrelated families with SCAR21. They reported 2 young adult sibs, born of unrelated parents of European origin, with an early-onset ataxia syndrome. At about 9 months of age, both patients developed recurrent episodes of liver failure, which were mainly associated with fever. Both sibs also had delayed early motor milestones and presented in early childhood with an ataxic gait, balance difficulties, and intention tremor, consistent with cerebellar dysfunction. Another patient, 17-year-old girl of Cuban descent, had a similar phenotype with early childhood onset of recurrent episodes of liver failure, progressive gait ataxia, and neurogenic stuttering. Delplanque *et al.* reported the identification of the causative gene in SCAR21, an autosomal-dominant disorder previously mapped to chromosome 7p21.3-p15.1 in French eight families.[5] In our case similarly, he had recurrent episodes of liver failure, delayed early motor milestones, ataxic gait, balance difficulties, intention tremor, optic atrophy, mild learning disability, and PNP in early childhood. We detected novel homozygous mutation SCYL1:C. 1420C>T in exon 11 of the SCYL1 gene. To the best of our knowledge, this is the first Turkish case of SCAR21 to present with ataxia. Table 1

**Table 1: The analysis of cases of SCAR21 from the literature and our patient**

| Patients | 1 | 2 | 3 | Our patient |
|---|---|---|---|---|
| Gender | F | M | F | M |
| Age | 20 y | 16 y | 17 y | 10 y |
| Descent | European | European | Cuban | Turkish |
| Clinical features | | | | |
| No. of recurrent episodes of liver dysfunction (age at first episode to age at last episode) | 5 (9 months to 11 years) | 3 (9 months to 6 years) | 3 (18 months to 3 years) | 2 (9 months to 2 years) |
| Walking independently (months) | 17 | 24 | 12 | 24 |
| Cognition | Normal | Mild intellectual disability | Mild learning disability | Mild learning disability |
| Cerebellar oculomotor disturbance | + | + | saccadic pursuit | vertical gaze palsy |
| Gait ataxia (onset) | + (early childhood) | + (early childhood) | + (childhood) | + (early childhood) |
| Spasticity | - | - | + | - |
| Tremor | + | + | + | + |
| Hepatosplenomegaly | + | + | + | - |
| Laboratory findings | | | | |
| Electroneurophysiology | ND | ND | axonal neuropathy | axonal neuropathy |
| Brain MRI | | | | |
| Cerebellar vermis atrophy | + | + | + | + |
| Optic nerve thinning | + | + | ND | + |

F=Female, M=Male, ND=Not determined

presents the analysis of cases of SCAR21 from the literature and our patient.

## Conclusion

Hereditary cerebellar ataxias are genetically heterogeneous disorders characterized by clinically variable gait disturbances and often accompanied by additional neurological symptoms and involvement of other organs. SCAR21 should be considered in the differential diagnosis of ataxia when additional recurrent episodes of liver failure, delayed early motor milestones, optic atrophy, and PNP.

### Consent

Informed consent was obtained from the parents of the child included in the study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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