***Chapter 6***
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# Homozygous Mutation of the AP4E1 Gene as a Cause of Autosomal Recessive Spastic Paraplegia Type 51 (SPG51) in a 17-Years-Old Boy

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## ABSTRACT

Autosomal recessive spastic paraplegia-51 (SPG51) is a rare neurodevelopmental disorder caused by a homozygous mutation in the AP4E1 gene, located on chromosome 15q21. SPG51 is characterized by neonatal hypotonia that progresses to hypertonia and spasticity. This is an often underdiagnosed condition in childhood, frequently presenting with clinical inconsistencies that can lead to misdiagnosis. Due to clinical overlap with conditions like cerebral palsy and other hereditary spastic paraplegias (e.g., SPG47, SPG50, SPG52), SPG51 is frequently underdiagnosed. Mutations in the AP-4E1 gene on chromosome 15q21.2 can lead to SPG51. Different mutations in this gene have been identified in affected individuals, leading to disruption of the AP4 complex and vesicular trafficking processes. The specific characteristics of SPG51 are, due to only a few cases, not well understood, due to limited reports of affected families. Affected individuals also have global developmental delay with impaired intellectual development and poor or absent speech. They typically present with hypotonia in the neonatal period, which progresses to muscular hypertonia, especially in the lower limbs. They may also exhibit contractures, talipes equinovarus, decreased muscle mass, short stature, and microcephaly. Severe mental retardation, absent speech, and dysmorphic facial features are common. Some patients may experience seizures. Neurological examination often reveals spastic paraplegia of the lower limbs, and brain imaging may show atrophy of the cerebellar vermis and cortical atrophy.

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This study presents an extremely rare case of a 17 years-old boy with autosomal recessive spastic paraplegia type 51. A compound heterozygous mutation in the AP4E1 gene was found in genetic analysis. The most disruptive symptoms were severe episodes of restlessness and aggression, particularly triggered by unfamiliar people and environments, including within the home. This case highlights the phenotypic variability of SPG51 and the importance of genetic testing and careful clinical evaluation in suspected cases of hereditary spastic paraplegia for accurate diagnosis.

*Keywords: Autosomal recessive; SPG51; mutation; hypotonia; hypertonia.*

## 1. INTRODUCTION

Hereditary spastic paraplegia (HSP) is a myriad of monogenic neurological defects aiding corticospinal and dorsal spinal cord axonal atrophy with a prevalence of 0.1–9.6 instances in every 100,000 around the world (Damiani et al., 2024). More than 90 SPG (for “SPastic parapleGia”) loci/genes have been identified, and the number will continue to grow as long as new sequence technologies are used in clinical laboratory practice (Meyyazhagan & Orlacchio, 2022).

HSP is a group of genetically and clinically heterogeneous neurodegenerative disorders characterized primarily by spasticity and weakness in the lower limbs (Bittmann, 2024). It includes four genetic inheritance forms: autosomal dominant inheritance (AD), autosomal recessive inheritance (AR), X-linked inheritance, and mitochondrial inheritance. HSP patients may have either pure or complicated HSP, differing based on symptoms. Patients with pure HSP simply develop spasticity and weakness of the lower limbs, while patients with complicated HSP are often accompanied by other symptoms, such as early cognitive impairment, ataxia, visual disturbance, macular degeneration, dysarthria, and callosal agenesis” (Lai et al., 2023). Autosomal recessive mutations in the AP-4 (adaptor protein complex 4) complex subunit ϵ − 1 (AP4E1) gene on chromosome 15q21.2 are known to cause spastic paraplegia 51 (SPG51), a recessive form of HSP (Niyoyita et al., 2025).

## 2. CASE REPORT

We present a case of a 17-years-old German boy with an autosomal recessive spastic paraplegia type 51 (SPG51), undefined variant. A compound heterozygous mutation in the AP4E1 gene was found in genetic exome sequencing (Bittmann, 2024). An unclassifiable epilepsy, most likely with complex focal seizures, is mostly present in SPG51. Perampanel was initiated as an anticonvulsant therapy after previous treatments with Sultiam, Lacosamide, Lamotrigine, Oxcarbazepine, Levetiracetam, and Zonisamide. SPG51 is a combined developmental disorder and a severe expressive language development disorder. Past medical history showed an epileptological situation quite stable, but general developmental delay. Head circumference was normal. No major seizure events were observed anymore; occasionally, episodes of smacking occur, which were interpreted differently. These episodes were hardly noticeable and very brief with a duration

of less than a minute. The current medication consisted of Baclofen 10-0-20 mg and Perampanel 3.5 mg. The main problem affecting both school and especially the home environment was extreme episodes of restlessness and aggression, provoked by unfamiliar people and environments. They also occur in the home environment. Examination findings included the patient in a fairly good general condition, quite communicative, but mostly with non-verbal communication (Bittmann, 2024). Muscle tone increasingly spastic distally and leg- dominant, there were no side differences, no clearly recognizable cranial nerve abnormalities. The EEG showed a polymorphic mixed wave rhythm, emphasized in the upper theta frequency spectrum. The amplitudes barely exceeded 70 volts. An on/off effect was hardly discernible. Plenty of muscle activity overlayed, but no specific pathological patterns, especially no seizure predisposition, were found. The assessment and recommendations included that the epileptological situation was not the main focus; rather, the behavioral disorder was hardly bearable.

## 3. DISCUSSION

“Most of all hereditary spastic paraplegias (HSP) are classified due to the genetic loci that are classified by numbers according to their discovery (Abou Jamra et al., 2011; Kong et al., 2013; Moreno-De-Luca et al., 2011; Manoochehri et al., 2022). Four types are described in HSP and have been related to disturbances of different adaptor protein complex subunits” (Manoochehri et al., 2022). “The functional loss of the AP-4 protein complex is the molecular mechanism in all AP-4 HSP disorders (Manoochehri et al., 2022; Ebrahimi-Fakhari et al., 2020). AP-4-associated hereditary spastic paraplegia (HSP) is a group of progressive neurodegenerative disorders that typically present in infancy or early childhood. Spastic paraplegia type 51 is a genetic disorder characterized by the degeneration and dysfunction of certain nerve tracts (Abou Jamra et al., 2011; Kong et al., 2013; Moreno-De-Luca et al., 2011; Manoochehri et al., 2022; Abdollahpour et al., 2015; Chowet al., 2021). The AP-4E1 subunit is involved in recognizing and binding sorting signals within cells, which is crucial for proper protein localization in neurons (Bittmann, 2024). It is involved in sorting proteins to specific cell membranes and establishing protein localization in neurons” (Manoochehri et al., 2022; Sager et al., 2022). The AP4E1 gene encodes a member of the adaptor complex large subunit protein family, which are essential components of adaptor protein complexes involved in vesicle formation and sorting of integral membrane proteins in the secretory and endocytic pathways (Chow et al., 2021; Winkler et al., 2021; Sager et al., 2022; Rudenskaya et al., 2021; Ebrahimi-Fakhari et al., 2020; Ebrahimi-Fakhari et al., 2018; Hatsugai et al., 2018). The encoded protein is a large subunit of adaptor protein complex-4, associated with both clathrin- and nonclathrin-coated vesicles. Mutations in this gene may be linked to cerebral palsy. Multiple isoforms of this gene have been identified due to alternative splicing. This gene is expressed ubiquitously, including in lymph nodes (Tüysüz et al., 2014; Wang et al., 2013; Kong et al., 2013; Castro et al., 2024; İpek et al., 2024; Ebrahimi-Fakhari et al., 2020; Ortega Suero et al., 2021; Damiani et al., 2024). AP4 complex-mediated trafficking is essential for brain development, with the AP4E1 gene encoding the AP-4 adaptor protein complex subunit ϵ−1 (Bittmann, 2024). Knock-out mice with mutations in this gene exhibit abnormal white blood

counts, enlarged lateral ventricles, a smaller corpus callosum, and hypoferremia. The clinical phenotype observed in this study aligns with previous reports of SPG51. Further mutational analysis and evaluation of AP4E1 in individuals with spastic paraplegia and their families are warranted to assess the disorder's frequency (Winkler et al., 2021; Sager et al., 2022; Rudenskaya et al., 2021; Ebrahimi-Fakhari et al., 2020).

This condition is often mistaken for cerebral palsy, but differs in its association with parental age and birth order (Abdollahpour et al., 2015; Rudenskaya et al., 2021; Wang et al., 2013). Symptoms include hypotonia progressing to spasticity, leading to difficulty walking or standing (Bittmann, 2024). Upper extremities may also be affected, resulting in spastic tetraplegia (Ebrahimi-Fakhari et al., 2018; Hatsugai et al., 2018; Tüysüz et al., 2014; Wang et al., 2013; Kong et al., 2013; Castro et al., 2024; İpek et al., 2024). “Other complications include bladder and bowel dysfunction, dysphagia, foot deformities, and contractures” (Moreno-De-Luca et al., 2011; Rudenskaya et al., 2021; Hatsugai et al., 2018; Wang et al., 2013). “Seizures occur in about half of patients, and the condition is associated with microcephaly and developmental delays. Speech development is delayed or absent, and stuttering could be rarely found” (Chow et al., 2021). One case report describes the genetic defect with a mycobacterial disease (Kong et al., 2013; Bittmann, 2024).

## 4. CONCLUSION

SPG51 is a rare and often underdiagnosed condition in childhood, frequently presenting with clinical inconsistencies that can lead to misdiagnosis. This case highlights the importance of genetic testing and careful clinical evaluation in suspected cases of HSP (Bittmann, 2024).

## CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

It is not applicable.

## DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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