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Mini Review

# Mini Review on Spinocerebellar Ataxia 27B (SCA27B)

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## Abstract

Spinocerebellar ataxia 27B (SCA27B) has recently been identified as a common cause of late-onset hereditary cerebellar ataxia. This brief review highlights key insights from the recent article by Abou Chaar et al., "Clinical, Radiological and Pathological Features of a Large American Cohort of Spinocerebellar Ataxia (SCA27B)," and discusses recent advances in understanding this disease. SCA27B is caused by intronic GAA repeat expansions of FGF14. The study confirms SCA27B as a leading cause of late-onset cerebellar ataxia in the U.S., with clinical, radiological, and pathological features consistent with international data. Its hallmark, a late-onset pan cerebellar syndrome with episodic symptoms, downbeat nystagmus, and predominant vermian atrophy, is clinically recognizable with high accuracy, enabling targeted genetic testing and early treatment. Early studies suggest this disease is highly responsive to 4-aminopyridine, making SCA27B one of the few hereditary ataxias that could be treatable. Nonetheless, validation through large-scale randomized controlled trials remains necessary.

**Keywords:** Spinocerebellar ataxia, 4-aminopyridine, Repeat expansions, Genetics, Cerebellum, Purkinje cells

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## Introduction

This study provides the first comprehensive characterization of SCA27B in the United States, examining 102 patients from five academic centers and offering important insights into disease prevalence, clinical manifestations, neuropathology, and therapeutic response in a US population **[1].** The diagnosis of Late-Onset Cerebellar Ataxia (LOCA) underwent a paradigm shift in 2023 with the discovery that intronic GAA repeat expansions in the Fibroblast Growth Factor 14 (FGF14) gene cause Spinocerebellar Ataxia type 27B (SCA27B) **[2,3].** This breakthrough filled a long-standing diagnostic gap, as SCA27B now accounts for 10-61% of previously unsolved LOCA cases across ethnically diverse populations **[2,4].**

### Genetic architecture and diagnostic difficulties

SCA27B is caused by GAA repeat expansions located approximately 526 kilobases within intron 1 of FGF14 **[2,3].** The pathogenic threshold was initially established at ≥ 250 GAA repeats, with expansions of 250-300 repeats showing incomplete penetrance and those ≥ 300 repeats demonstrating full penetrance **[2,3].** Recent data from a large French-Canadian cohort suggest that even (GAA) 200-249 alleles may be pathogenic in some patients, supporting the need to reevaluate pathogenic thresholds **[5]**. The deep intronic location explains why SCA27B evaded detection by conventional genetic testing approaches, requiring either whole-genome sequencing with specialized bioinformatic analysis or targeted FGF14 trinucleotide repeat analysis **[4]**.

A notable feature of SCA27B genetics is the parent-of-origin effect on repeat transmission. Maternal transmission tends to increase the size of repeat expansions, while paternal transmission causes contraction, sometimes to sub pathogenic allele sizes **[3]**. This germline instability explains several epidemiological features: the high proportion of apparently sporadic cases (approximately half lack family history), generation-skipping through paternal inheritance, and reduced male transmission **[2]**.

### Clinical phenotype: The US experience

This study characterized 102 US patients with genetically confirmed SCA27B, representing the largest single-country cohort reported to date **[1]**. The mean age at onset was 57 ± 12.5 years, consistent with the 50-70-year range reported in other cohorts **[1,2]**. The disease presented as a slowly progressive pan cerebellar syndrome, with balance and gait impairment almost universally present at disease onset **[1]**.

### Episodic symptoms

A hallmark feature identified in the US cohort was the occurrence of episodic symptoms in 51% of patients **[1]**. These episodes consist of variable combinations of diplopia, vertigo, dysarthria, and ataxia lasting from minutes to days, with common triggers including alcohol intake and exercise **[2]**. The episodic nature can lead to initial misdiagnosis, with some patients receiving diagnoses of transient ischemic attack or acute peripheral vestibular syndrome **[4,6]**.

### Cerebellar oculomotor signs

Downbeat nystagmus represents an important diagnostic feature, observed in 37-50% of patients across cohorts **[1,2,7,8]**. Clinical phenotyping focusing on downbeat nystagmus with or without ataxia achieved a diagnostic success rate of 90% in patients with onset after age 45 **[8]**. Video-oculography has been recognized as a valuable diagnostic tool, with downbeat nystagmus significantly more frequent in FGF14-GAA expansion carriers than non-carriers (92% vs. 33%) **[9]**.

### Associated features

Additional clinical features include postural tremor (22-28%), vestibular hypofunction, pyramidal signs (8%), and autonomic dysfunction (28%) **[1,2,7]**. Some patients display mild axonal peripheral sensory or sensorimotor neuropathy, though polyneuropathy is not a core feature **[2]**. Cognitive impairment remains infrequent even in advanced stages, distinguishing SCA27B from many other neurodegenerative ataxias **[10]**.

### Survival

This study is among the first to examine overall survival in patients with SCA27B. The findings indicate that SCA27B does not substantially affect lifespan (median survival was 39 years from disease onset), consistent with previous studies **[11]**.

### Radiological features

In this study, 93% (80/86) of patients had cerebellar atrophy on routine MRI, similar to other studies reporting variable degrees of cerebellar atrophy in 74-97% of patients **[1,3,8]**. The atrophy is most pronounced in the cerebellar vermis and paravermis regions **[1]**. A distinctive imaging finding is the superior cerebellar peduncle sign, present in approximately 68% of patients, which may aid in diagnosis **[6,12]**. Non-specific white matter abnormalities are frequently observed (>90%), though their clinical relevance remains unclear **[6]**.

MR spectroscopy of the cerebellum shows a progressive decline in NAA/Cr ratios in the cerebellar hemisphere over time, but not the vermis, suggesting a potential biomarker of disease progression **[7]**.

## Neuropathological findings: Novel insights from the US cohort

This study provided critical neuropathological data from four brain specimens of patients with genetically confirmed SCA27B, representing one of the largest neuropathological series reported to date **[1]**. The principal finding was loss of Purkinje neurons that was most severe in the vermis, particularly in the anterior vermis **[1]**. This pattern confirms and extends findings from earlier European neuropathological examinations, which demonstrated cerebellar atrophy more prominent in the vermis than in the hemispheres **[3]**.

Microscopic analysis shows widespread depletion of Purkinje cells, gliosis in the molecular layer, and mild overall cell loss in the granule-cell layer **[1,3]**. The cerebellar hemispheres show relatively preserved granule cell density and less prominent molecular layer gliosis than the vermis **[3]**. The "empty basket" appearance on silver staining reflects the loss of Purkinje cells while their surrounding basket cell processes stay intact **[3]**.

FGF14 is expressed throughout the central nervous system, most abundantly in cerebellar granule and Purkinje cells. It plays a key role in the spontaneous rhythmic firing of Purkinje cells by regulating and promoting localization of voltage-gated sodium channels at the axon initial segment **[3]**. Preliminary investigations of patient-derived postmortem cerebellum and induced pluripotent stem cell-derived motor neurons show reduced FGF14 RNA and protein expression in patients compared to controls, supporting a loss-of-function mechanism **[2,3]**.

The pathogenic mechanism likely involves transcriptional interference caused by the intronic GAA expansion, consistent with FGF14's high intolerance to loss-of-function mutations **[3]**. This mechanism resembles the pathophysiology of Friedreich's ataxia, which involves a similar intronic GAA expansion in the FXN gene **[2]** Impairment of ion-channel kinetics is consistent with the frequent episodic presentation, suggesting that SCA27B may represent a type of channelopathy **[3]**.

**Therapeutic response to 4-aminopyridine**

A therapeutic advance highlighted by this study is the recognition that many SCA27B patients respond to 4-aminopyridine (4-AP) treatment. In the US cohort, 75% (21/28) of treated patients reported a positive treatment response **[1]**. This finding is consistent with international cohorts reporting subjective symptom improvement in 54-86% of treated patients **[5,7,10]**.

Prospective n-of-1 treatment studies with on/off design showed a significant reduction in daily symptomatic time and symptom severity on 4-AP10. Other studies reported clinically meaningful improvement in 71% of patients treated with 4-aminopyridine **[8]**. Objective stabilization and/or improvement on MR spectroscopy has also been documented with 4-AP treatment **[7]**.

The mechanism underlying 4-AP responsiveness likely involves FGF14's regulation of voltage-gated sodium and potassium channels at the axon initial segment of Purkinje cells. 4-Aminopyridine, a potassium channel blocker, may partially compensate for the ion channel dysfunction caused by FGF14 loss-of-function **[3,10]**. This therapeutic response is particularly notable given that 4-AP has demonstrated benefit in episodic ataxia type 2 (EA2) in randomized controlled trials **[13]**.

## Discussion & Conclusion

This study establishes SCA27B as a major cause of late-onset cerebellar ataxia in the United States, with clinical, radiological, and pathological features consistent with those reported in international cohorts **[1]**. Given the high diagnostic yield of SCA27B testing in LOCA, particularly in patients with episodic symptoms and downbeat nystagmus, targeted FGF14 GAA repeat expansion testing should be considered early in the diagnostic evaluation **[1,4]**. The deep intronic location requires specific testing approaches beyond standard exome sequencing **[4]**. The characteristic phenotype-late-onset pan cerebellar syndrome with episodic symptoms, downbeat nystagmus, and predominant vermian atrophy-can be recognized clinically with high accuracy (up to 90% in selected cohorts), allowing targeted genetic testing and early therapeutic intervention **[8]**. The high rate of 4-aminopyridine responsiveness (54-86% across cohorts) represents a major advance, as SCA27B may be one of the few treatable forms of hereditary ataxia **[1,5,7,10]**. However, validation in large-scale randomized controlled trials is needed.

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