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Novel compound heterozygous mutations in *CWF19L1* in a 3-year-old girl with SCAR17

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Background

- Spinocerebellar ataxia, autosomal recessive 17 (SCAR17) is an exceedingly rare neurodegenerative disorder caused by biallelic pathogenic variants in the *CWF19L1*.
- To date, only about **13 cases** have been reported globally.
- While the classic phenotype includes early-onset ataxia, global developmental delay, and epilepsy, the full clinical spectrum remains poorly defined.

Case Report

- A 3-year-old girl, born to non-consanguineous parents, presented with ataxic gait, toe-walking with ankle inversion, and dysarthria.
- Intermittent bilateral intention tremors were observed during goal-directed movements.
- Unlike previously reported SCAR17 patients (typically walking at ≥18 months, often with developmental regression), she achieved independent walking at 13 months and showed no regression.
- The Bayley Scales of Infant and Toddler Development (corrected age 42.5 months) revealed preserved cognitive and language function, with mild motor delay.
- Berg Balance Scale (BBS) score was 41 points, reflecting a mild-to-moderate balance impairment consistent with cerebellar involvement.
- She had a history of two simple febrile seizures, without evidence of epilepsy, and no nystagmus.
- Brain MRI demonstrated cerebellar atrophy.

Fig. 1. Brain MRI of the patient at age 3 showing atrophy of the cerebellum

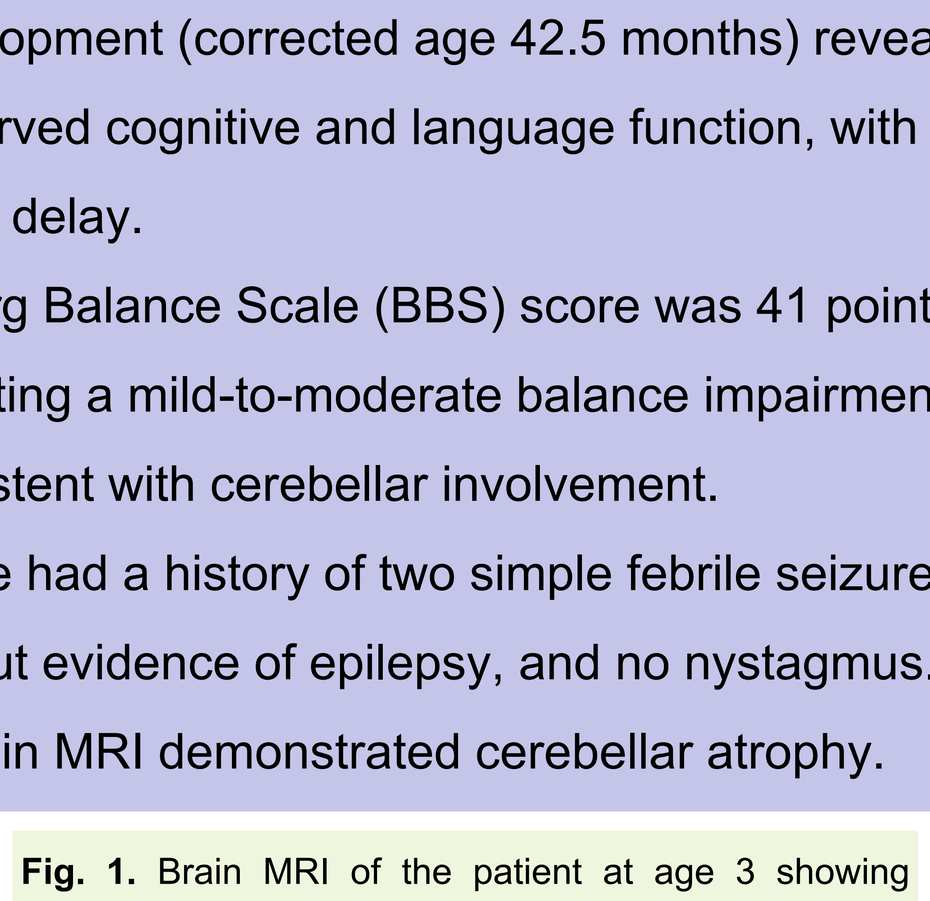

Table 1. Genotype-phenotype correlation in reported SCAR17 cases

Features	Truncating only (N=7)	Missense homozygous (N=2)	Missense heterozygous (N=4) *including the current case*
Genetics	Nonsense / Frameshift / Splice	Missense homozygous	Compound heterozygous with ⩾1 missense allele
Cognitive	Intellectual disability	Borderline / Normal	Borderline / Preserved
Language	Delayed / Dysarthric	Sentences with dysarthria	Variable / Preserved
Motor Development	Variable delay	Mildly delayed	Mild delay & ataxia
Epilepsy	Variable	Late-onset / Controlled	Absent / Controlled
Brain MRI	Marked cerebellar & brainstem atrophy	Cerebellar atrophy	Mild or no cerebellar atrophy
Regression	Variable	Motor regression	None or minimal
Phenotypic Severity	Moderate – Severe	Mild – Moderate	Mild

Genetic Study

- Trio whole-exome sequencing (WES) identified two novel compound heterozygous variants in the *CWF19L1*: a paternally inherited nonsense variant (NM_018294.6: c.576C>A, p.Tyr192Ter) and a maternally inherited missense variant (NM_018294.6: c.1241A>G, p.His414Arg).
- Both parents were confirmed as heterozygous carriers.

Discussion

- Previously reported CWF19L1 pathogenic variants were predominantly truncating, typically associated with intellectual disability and developmental regression.
- This patient, harboring a compound heterozygous nonsense and missense variant, presented with a remarkably milder phenotype with preserved cognition and no epilepsy.
- This suggests that a missense allele may attenuate disease severity by preserving partial protein function.

Conclusion

- This case significantly expands the genetic and phenotypic spectrum of SCAR17.
- *CWF19L1*-related disorder should be considered in the differential diagnosis even in patients presenting with a mild cerebellar phenotype, as the clinical spectrum may be broader than previously recognized.