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SHORT REPORT

Expansion of the phenotypic and molecular spectrum of CWF19L1-related disorder

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Abstract

Pathogenic variants in *CWF19L1* lead to a rare autosomal recessive form of hereditary ataxia with only seven cases reported to date. Here, we describe four additional unrelated patients with biallelic variants in *CWF19L1* (age range: 6–22 years) and provide a comprehensive review of the literature. The clinical spectrum was broad, including mild to profound global developmental delay; global or motor regression in infancy or adolescence; childhood-onset ataxia and cerebellar atrophy; and early-onset epilepsy. Since only two previously reported patients were adults, our cohort expands our understanding of the evolution of symptoms from childhood into early adulthood. Taken together, we describe that CWF19L1-related disorder presents with developmental and epileptic encephalopathy with treatment-resistant seizures and intellectual disability in childhood followed by progressive ataxia and other extrapyramidal movement disorders in adolescence.

KEYWORDS
ataxia, cerebellar malformation, CWF19L1, epilepsy

1 | INTRODUCTION

The autosomal recessive cerebellar ataxias (ARCA) are diseases of great genetic heterogeneity and encompass complex clinical phenotypes, in which ataxia is a common feature. In addition to prominent ataxia, ARCAs are often associated with developmental delay (DD), intellectual disability (ID), epilepsy, extra-pyramidal movement disorders, behavioral problems, peripheral neuropathy, and cerebellar degeneration demonstrated by neuroimaging or pathology.[1]

While most subtypes of ARCA are individually rare, the recessive ataxias are cumulatively not uncommon, with an estimated frequency of 1/20.000 that varies between countries.[2] CWF19-like cell cycle

control factor 1 (*CWF19L1*) is one of the 59 ARCA-associated genes,[1] located on chromosome 10q24.31. CWF19L1 is believed to be involved in cell cycle control, endosomal trafficking and possibly also mRNA processing.[3] *CWF19L1* is a rare cause of ARCA and to date, only seven cases from four unrelated families have been reported.[2–5] Of these seven patients[2–5]; one was a terminancy of pregnancy, four were children between 6–14 years at time of publication[2,5] while two were adults in their thirties.[3] Common manifestations include motor development ranging from normal[3,5] to mildly delayed,[2,4] and cognitive level ranging from normal in a single case[2] to borderline[3] or mild ID[2,4,5] in two and three patients, respectively. All patients presented with ataxia with the age at onset ranging from birth[2] or early childhood[4,5] in four patients and up to the third decade in two adults.[3] Epilepsy was only reported in the two adult siblings, presenting with focal tonic seizure with impaired awareness; both had onset of seizures during their second decade and became seizure free on monotherapy.[3]

Here, we describe four unrelated patients with biallelic variants in *CWF19L1*, and delineate the phenotypic spectrum of the disease.

2 | METHODS

2.1 | Study cohort

GeneMatcher[6] was used to gather clinical and molecular information from patients with a CWF19L1-related disorder. Data were collected through the treating physician using a customized clinical table that included, but was not limited to, birth and pregnancy information, developmental and cognitive milestones, brain images, physical examinations, as well as indication of behavioral and psychiatric comorbidities, epilepsy and congenital malformations.

2.2 | Ethics

The study was conducted in agreement with the Declaration of Helsinki and approved by the local ethics committees. Informed consent was given from parents or legal guardians (when applicable).

2.3 | Genetic identification and analysis

Probands were investigated by whole exome sequencing requested by the treating physician while the segregation studies were performed using Sanger sequencing. The variants in *CWF19L1* were annotated using the transcript NM_018294.5 (GRCh37/hg19), and classified according to the 2015 American College of Medical Genetics and Genomics guidelines.[7] Genome Aggregation Database (gnomAD)[8] was used to obtain the frequency of each variant that were described according to HGVS-nomenclature recommendations using Mutalyzer software (https://mutalyzer.nl/).

3 | RESULTS

We report four unrelated patients with a CWF19L1-related disorder; one child, one adolescent and two adults. See Table 1 for summary of clinical data and supplementary file for additional clinical information.

3.1 | Patient 1

Patient 1 is a 16-year-old female, born to consanguineous Turkish parents. Pregnancy and birth were uncomplicated. First concerns arose at 12 months of life when she presented with febrile status epilepticus. At this point, she was able to hold her head, sit, crawl, and say single words. After seizure onset, her development regressed with poor eye contact, feeding difficulties and inability to sit and crawl.

Over the following years, the patient experienced recurrent febrile seizures that evolved into unprovoked focal seizures.

At 2 years of age the interictal EEG showed a normal background, with multifocal interictal epileptiform discharges. Since the age of 3 years, serial EEGs documented a progressive deterioration of the background activity that became slower and disorganized (Figure 1A, B). Ictal EEG recordings documented focal onset seizures (Figure 1C). Seizures remained resistant despite trials of several anti-seizure medications (ASM) and the patient continues to have weekly hemiclonic seizures as well as sporadic atypical absences (Figure 1C).

Brain MRI performed at age 9 years showed cerebellar hypoplasia and delayed myelination in the temporal lobes. A second MRI at 13 years showed normal myelination, unchanged cerebellar hypoplasia (Figure 2A, B) but also hypotrophy of the brainstem as well as a pituitary adenoma (Figure 2C), clinically associated with pituitary insufficiency.

Whole exome sequencing (WES) revealed a homozygous disease causing frameshift variant in *CWF19L1*; c.467delC; p.(Pro156-Hisfs*33). The finding was confirmed by sanger sequencing. The variant was not previously reported in GnomAD[8] and was found in heterozygous state in both parents. The variant has previously been reported in another Turkish patient with an CWF19L1-related disorder[4] and is predicted to be likely pathogenic (PVS1 and PM2).

3.2 | Patient 2

Patient 2 is a 6-year-old male. The pregnancy was uneventful and he was born at term by cesarean section due to transversal lie. Apgar scores, weight and height at birth were normal. The parents were first degree cousins of Turkish descent. Their second child was stillborn.

First concerns were raised at 24 months of life due to an unsteady gait and speech delay. Over the following years, global DD became evident, resulting in mild ID, severe speech delay, and ataxia affecting gross and fine motor skills. He currently communicates using

TABLE 1 Clinical and genetic overview of patients with biallelic variants in *CWF19L1*

Family	1	2	3	4	5		6	7		8	
ID number	Current P1	Current P2	Current P3	Current P4	P5 (Burns et al., 2014)	P6 (Burns et al., 2014)	P7 (Nguyen et al., 2016)	P8, sibling of P9 (Evers et al., 2016)	P9, sibling of P8 (Evers et al., 2016)	P10, sibling of P11 (Algahtani et al., 2021)	P11, sibling of P10 (Algahtani et al., 2021)
Sex	Female	Male	Female	Male	Male	Female	Female	Male	Female	Female	Female
Age	16 y	6 y	21 y	21 y	12 y	6 y	10 y	14 y	Termination of pregnancy 22 w	33 y	29 y
DNA change (NM_018294.5)	c.467delC; c.467delC	c.605dup; c.605dup	c.708+1G>A; c.708+1G>A	c.820dup; c.1394C>T	c.964+1G>A; c.964+1G>A)	c.964+1G>A; c.964+1G>A)	c.37G>C; c.946A>T	c.467delC; c.467delC	c.467delC; c.467delC	c.395A>G; c.395A>G	c.395A>G; c.395A>G
Protein change	p.(Pro156Hisfs*33); p.(Pro156Hisfs*33)	p.Tyr202*p.Tyr202*	p.(?); p.(?)	p.(Ser274Phefs*20); p.(Ala465Val)	p.(?); p.(?)	p.(?); p.(?)	p.Asp13His p.Lys316*	p.(Pro156Hisfs*33); p.(Pro156Hisfs*33)	p.(Pro156Hisfs*33); p.(Pro156Hisfs*33)	p.(Asp132Gly); p.(Asp132Gly)	p.(Asp132Gly); p.(Asp132Gly)
Inheritance	Heterozygous state in parents	Parents not testet	Parents not testet	Heterozygous state in parents	Heterozygous state in parents	Heterozygous state in parents	Heterozygous state in parents	Heterozygous state in parents	Heterozygous state in parents	Heterozygous state in parents	Heterozygous state in parents
Consanguinity	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Ethnic origin	Turkish	Turkish	Lebanese	Chinese	Turkish	Turkish	Dutch	Turkish	Turkish	Yemini	Yemini
Developmental delay	Severe	Severe	Yes, degree unknown	Severe	Mild	Mild	Normal	Mild	NA	Normal	Normal
Intellectual disability	Profound	Mild (50)	Mild	Mild (63) at 5y	No (90)	Mild (68)	Mild (55)	Mild (57), at 14y of life	NA	No (borderline)	No (borderline)
Age at walking	12 mths	2–3 y	20 mths	12 mths	20 mths	18 mths	18 mths	13 mths	NA	NA	NA
Present motor skills	Nonambulant.	Able to walk, truncal ataxia.	Able to walk, truncal ataxia.	Able to walk, truncal ataxia.	Able to walk, truncal ataxia, limb hypotonia.	Able to walk, truncal ataxia, limb hypotonia	Able to walk, truncal ataxia, limb hypotonia	Able to walk, truncal ataxia	NA	Able to walk, truncal ataxia	Able to walk, truncal ataxia
Age at first word	12 mths	1 y	12 mths	18 mths	NA	NA	NA	31 mths	NA	NA	NA
Current verbal capability	Non-verbal	Phrases, uses signs	Sentences	Follows simple commands. Responds to simple questions. Speech is moderately to severely dysarthric.	NA	NA	Sentences	Simple words	NA	Sentences	Sentences
Dysarthria	Non-verbal	No	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
Age at onset of dysarthria	Non-verbal	NA	4 y	NA	NA	NA	NA	NA	NA	33 y	29 y
Developmental regression	Global	No	Yes	Motor	No	No	Global	No	NA	Motor	Motor
Age of regression	At onset of seizure (12 mths) and again at 13 y	No	2 y	Adolescence	–	–	5 y	–	NA	30 y	29 y
Special needs or public school	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	NA	Drop out school at 15y	Drop out school at 15y

TABLE 1 (Continued)

Family	1	2	3	4	5		6	7		8	
ID number	Current P1	Current P2	Current P3	Current P4	P5 (Burns et al., 2014)	P6 (Burns et al., 2014)	P7 (Nguyen et al., 2016)	P8, sibling of P9 (Evers et al., 2016)	P9, sibling of P8 (Evers et al., 2016)	P10, sibling of P11 (Algahtani et al., 2021)	P11, sibling of P10 (Algahtani et al., 2021)
Epilepsy diagnosis	Yes	No	Yes	Yes	No	No	No	No	NA	Yes	Yes
Age at onset of seizure	12 mths	–	2 y	15 y	–	–	–	–	NA	20 y	29 y
Seizure type	Febril status. Focal hemiclonic. Atypical absences.	–	FBTCS	Unknown onset tonic clonic	–	–	–	–	NA	Focal tonic seizure with impaired awareness	Focal tonic seizure with impaired awareness
Seizure outcome	Treatment resistant	–	Treatment resistant	Seizure free with monotherapy (VPA)	–	–	–	–	NA	Seizure free with monotherapy (LMT)	Seizure free with monotherapy (LMT)
EEG findings	2 y: Normal 3 y: slow and disorganized with interictal multifocal spikes waves.	5 y: Intermittent slowing generalized and focal epileptiform interictal discharges posterior left.	5 y: focal right central epileptiform discharges 13 y: multifocal epileptiform discharges.	Epileptiform discharges middle frontal line, photosensitive reaction	–	–	–	–	NA	NA	Interictal bilateral temporal epileptic discharges
Brain MRI	9 y: Cerebellar hypoplasia and temporal hypomyelination. 13 y: normal myelination, unchanged cerebellar, hypoplasia, hypoplastic brainstem and pituitary adenoma.	3 y and 5 y non progressive cerebellar atrophy, mild periventricular hyperintensity	5 y and 13 y: Cerebellar atrophy, thin corpus callosum.	18 y: Cerebellar and caudado atrophy, hyperintensity of bilateral basal ganglia.	Cerebellar hypoplasia	Cerebellar hypoplasia	5 y: Cerebellar hypoplasia. 10 y: Cerebellar atrophy.	3 y 11mths: Cerebellar atrophy. 7 y 8mths: Progressive cerebellar atrophy. 9 y: Unchanged cerebellar atrophy.	Cerebellar hypoplasia/ agenesis corpus callosum.	30 y: Cerebellar atrophy.	29 y: Cerebellar atrophy.
Autistic features	Unable to evaluate	No	No	No	NA	NA	No	NA	NA	No	No
Tremor	Yes	No	Yes	No	NA	NA	Yes	Yes	NA	Yes	Yes
Ataxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
Age of onset ataxia	Before 2 y. Stable until progression at 13 y of life.	Congenital	4 y	4 y	Congenital	Congenital	5 y	3 y 10 m	NA	30 y	29 y
Movement disorders	No	No	No	Chorea, dystonia and segmental myoclonus	No	No	Dystonia	No	NA	No	No
Ophtalmo-logical anomalies	Poor eye contact, nystagmus.	No	Chorioretinal dysplasia	No	NA	NA	Oculomotor apraxia	NA	NA	Nystagmus	Nystagmus

(Continues)

TABLE 1 (Continued)

Family ID number	1 Current P1	2 Current P2	3 Current P3	4 Current P4	5 P5 (Burns et al., 2014)	P6 (Burns et al., 2014)	6 P7 (Nguyen et al., 2016)	7 P8, sibling of P9 (Evers et al., 2016)	P9, sibling of P8 (Evers et al., 2016)	8 P10, sibling of P11 (Algahtani et al., 2021)	P11, sibling of P10 (Algahtani et al., 2021)
Other	Microcephaly pituitary insufficiency	NA	Syndactyly hand fingers Scoliosis Hypopigmentation in right thigh	No	NA	NA	No	Congenital microcephaly	Vertebral malformation, polydactyly	NA	NA

Abbreviations: FBTCS, focal to bilateral tonic clonic seizures; LMT, lamotrigen; mths, months; NA, not available; P, patient; VPA, valproate acid; y, years; w, weeks.

short sentences and sign language. He is able to walk short distances independently and uses a wheelchair for longer distances. No developmental regression was reported.

He has not experienced epileptic seizures but an EEG undertaken at age 5.5 years showed generalized intermittent slowing and focal sharp waves at the temporo-occipital lobe. Brain MRI showed cerebellar atrophy and periventricular T2-hyperintensities.

WES identified a homozygous variant (c.605dup; p.(Tyr202*)) in *CWF19L1*. This variant was predicted to result in a premature stop at codon 202. The variant was not previously reported in GnomAD and is predicted to be likely pathogenic (PVS1 and PM2).

3.3 | Patient 3

Patient 3 is a 21-year-old female, born to consanguineous Lebanese parents. Pregnancy and birth were uncomplicated.

She learned to speak at 2 years of life, sat independently by the age of 9 months, and started walking around 20 months. Development remained normal before developing seizures at the age of 2 years with focal tonic seizure, bilateral clonic and focal to bilateral tonic clonic seizures.

At the age of 5 years, an EEG showed epileptiform discharges over the right central region associated with eyelid myoclonus. The EEG also showed epileptiform discharges over central regions which was associated with bilateral clonic movements. At the age 13 years the EEG showed multifocal epileptiform discharges, with bilateral frontal and central right predominance.

Current ASM include valproic acid and topiramate with a reduction in seizure frequency to weekly seizures.

Brain MRI performed at the age of 5 years showed a hypoplastic corpus callosum and reduced volume of the right cerebellar hemisphere and vermis. Additional brain MRI at 12 years showed progressive cerebellar atrophy.

WES identified a homozygous splice variant c.708+1G>A predicted to result in a skipping of exon 8 of *CWF19L1*. This variant is absent from GnomAD and is predicted to be likely pathogenic (PVS1 and PM2).

3.4 | Patient 4

Patient 4 is a 21-year-old male, born to non-consanguineous Chinese parents. He was born at term without any significant pre- or perinatal history.

First concerns arose before his second birthday when motor apraxia became evident. Neuropsychological evaluation at the age of 5 years revealed an IQ of 63. Over the course of several years, he developed a progressive movement disorder, consisting of generalized chorea, dystonia, segmental myoclonus, dysmetria, and ataxic gait. He currently walks short distances with support but otherwise requires a wheelchair. He speaks though with significant dysarthria, but is unable to read or write.

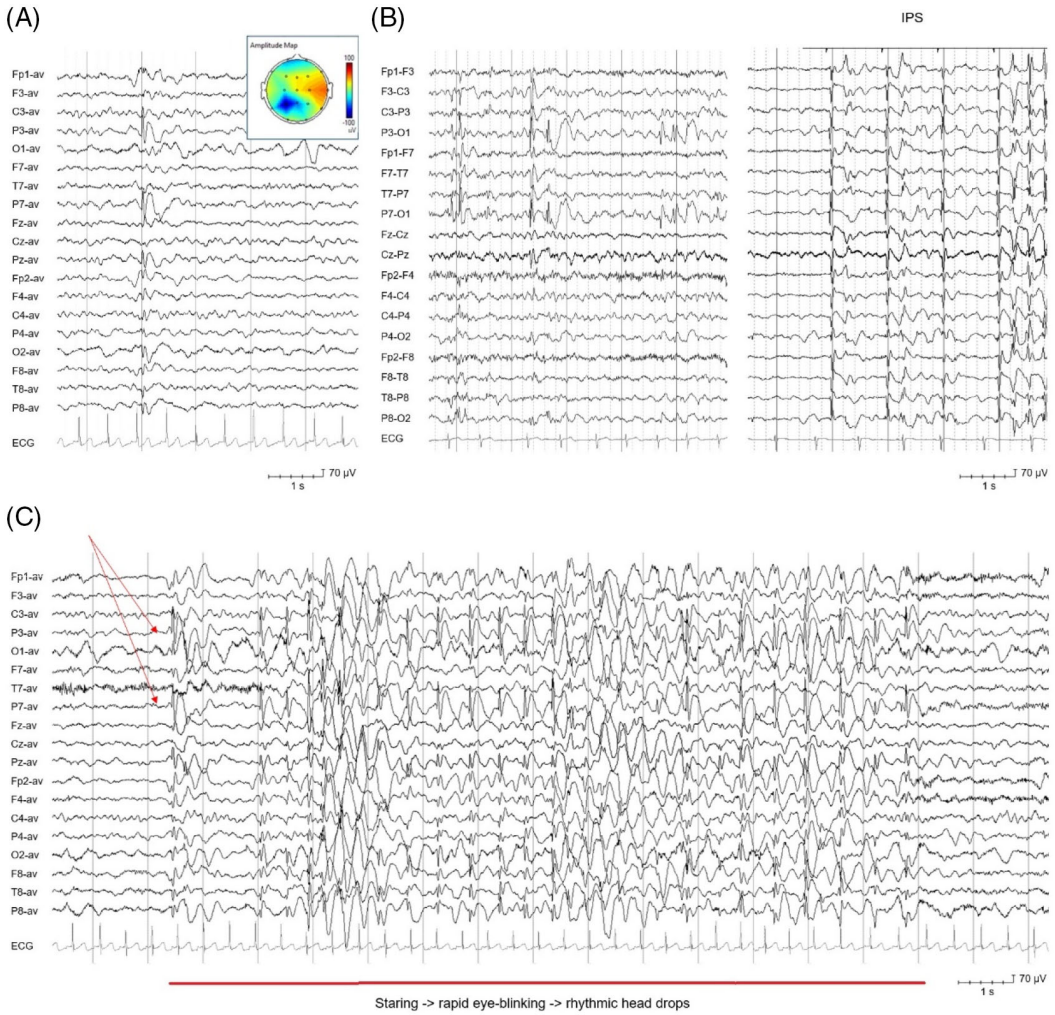

FIGURE 1 The interictal EEG showed (A) at the age of 3 years, a polymorphic delta activity in the occipito-parietal regions, bilaterally with left predominance, and high amplitude spike-and-slow waves in the left parieto-posttemporal region (max P3-P7) (B) the EEG that was progressively worsening over time also photo paroxysmal response at 1 Hz photic stimulation (4-years-old). The ictal EEG (C) during one of his typical seizures with staring, rapid blinking and rhythmic head drops/jerks showed diffuse 2–2.5 Hz spike and slow waves, with onset and maximum of amplitude in the right parieto-post temporal region [Colour figure can be viewed at wileyonlinelibrary.com]

At the age of 15 years, he had a tonic–clonic seizure of unknown onset. He had a similar event 6 months later, and was started on valproic acid. He has been seizure-free since. EEG at 18 years showed epileptiform discharges frontally in the midline and a photoparoxysmal response.

Brain MRI performed at 18 years showed symmetric T2 signal elevation in the basal ganglia, atrophy of the caudate bilaterally and reduced volume of the cerebellar hemispheres.

Exome sequencing identified compound heterozygous variants (c.820dup and c.1394C>T) in *CWF19L1*. The c.820dup (p.Ser274Phefs*20) was classified as likely pathogenic (PVS1, PM2). According to gnomAD allelic frequency is 0.00007 (21/282780). The variant c.1394C>T; p.(Ala465Val) was absent from gnomAD, had a CADD score of 23.9 and was located on well-established functional domain without benign variation. The variant was classified as a variant of unknown significance (PM1, PM2, and BP4).

4 | DISCUSSION

CWF19L1 is expressed throughout the brain and has been proposed to play a role in neuronal development.[2] It encodes several protein isoforms, which are postulated to have a role in cell cycle control, endosomal trafficking and mRNA processing.[2]

We here describe four novel unrelated patients with a CWF19L1-related disorder and review the literature. Symptoms in this rare and complex disorder include mild to profound global DD, epilepsy and/or motor regression, early-onset ataxia and extrapyramidal movement disorders, and cerebellar atrophy. The novel findings of our cohort include developmental and epileptic encephalopathy with infantile-onset and treatment-resistant seizures, profound global DD, extrapyramidal movement disorder and infantile onset ataxia that progresses in adolescence.

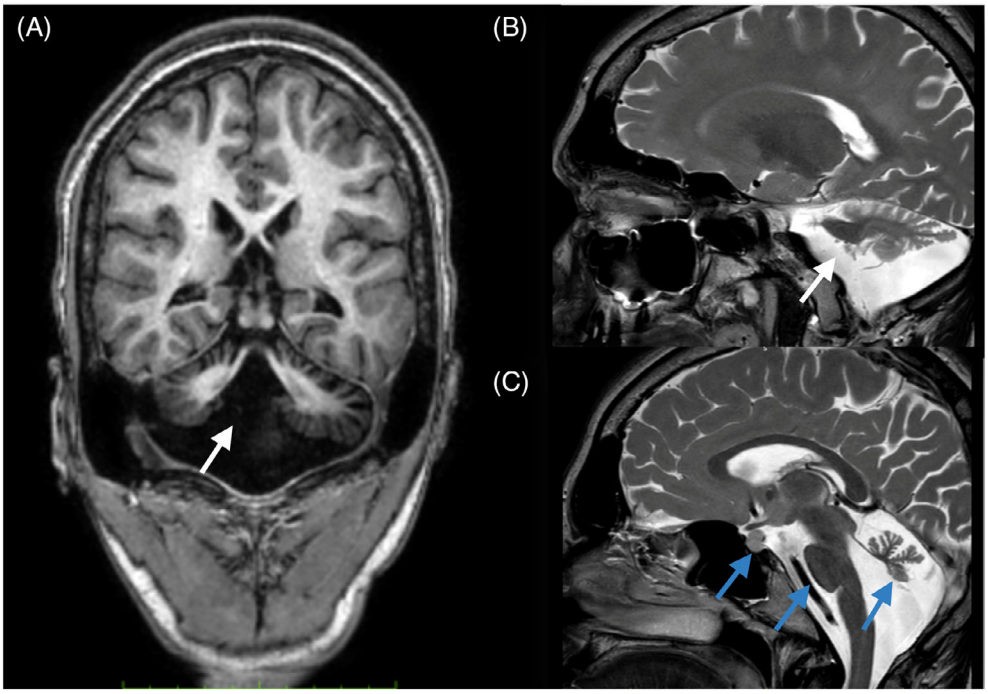

FIGURE 2 Brain magnetic resonance imaging of patient 1. Coronal T1 and sagital T2 imaging from 13 years of life, showing cerebellar hypoplasia affecting both vermis and the hemispheres (white arrows) (A and B). Sagital T2 showing pituitary adenoma and hypoplasia of the brainstem and cerebellum (blue arrows) (C) [Colour figure can be viewed at wileyonlinelibrary.com]

Evaluation of the 11 patients with biallelic variants in *CWF19L1* (Table 1) showed that nine patients had homozygous truncating variants while two unrelated patients carried compound heterozygous variants. Of the five variants in the homozygous state (c.395A>G; c.467delC; c.605dup; c.708+1G>A; and c.964+1G>A), only the c.467delC variant was recurrent and present in two Turkish families (family 1 and 7). The two families encompass three affected cases of which one was a termination of pregnancy; while both liveborn patients exhibited global DD, developmental regression during childhood, ataxia, and brain malformations (Table 1), P1 was much more severely affected in terms of global development and also had epilepsy. Although both patients underwent trio exome sequencing and no other (likely) pathogenic variants were detected, it is not unlikely that other modifier genes could have influenced the natural history of this rare disorder. Additional families with the same variant are needed to further explore the phenotypical spectrum and better understand if and why there might be a phenotypical spectrum. In addition, the fact that the c.467delC was found in two Turkish families suggest that the variant might be a founder pathogenic variant in Turkey and that it might be found in other Turkish families with genetically unsolved ataxia.

The combined evaluation of our cohort alongside the seven previously published patients[2–5] shows that epilepsy was present in 5/10 live-born patients; our three patients (P1 and P3-4) and two previously published adults (P10-P11).[3] While P4 and P10-11 experienced seizure onset at age 15, 20 and 29 years, respectively, P1 and P3 started before their second birthday; in addition, P1 and P3 were the only two patients with treatment resistant seizures. The epilepsy syndrome of patients P4 and P10-11 could be classified as "developmental encephalopathy and epilepsy"[9,10] due to the adolescence/adulthood-onset and treatable seizures without regression in development at time of seizure-onset; on comparison, the epilepsy syndrome of P1 and P3 would fit a developmental and epileptic encephalopathy due to the early-onset and treatment-resistant seizures, the disorganized EEG background and the developmental regression at seizure onset.[10]

All 10 liveborn patients had ataxia and symptoms either began in infancy (P1-P8)[2,4,5] or in the second decade of life.[3] Interestingly, P1 was the only patient to experience a biphasic regression as her ataxia started before the second birthday and remained stable until 13 year of life when it progressed and rendered her non-ambulant.

In summary, *CWF19L1* causes a rare and complex type of autosomal recessive ataxia associated with a range of neurodevelopmental features that often start in early childhood. Larger cohorts are needed to further explore the phenotypical spectrum, identify genotype–phenotype correlations and delineate the natural history.

AUTHOR CONTRIBUTIONS

Conceptualization: Allan Bayat. *Data curation*: Mona Grimmel, Darius Ebrahimi-Fakhari, Victoria G. Paul, Allan Bayat. *Formal analysis*: Allan Bayat, Carolina Alvarez, Elena Gardella. *Investigation*: Allan Bayat, Mona Grimmel, Darius Ebrahimi-Fakhari, Victoria G. Paul. *Visualization*: Elena Gardella. *Supervision*: Allan Bayat, Rikke S. Møller. *Writing-original draft*: Allan Bayat, Carolina Alvarez. *Writing-review & editing*: all authors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14275.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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