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Juvenile Dentatorubral-Pallidoluysian Atrophy (DRPLA) in a Patient From Northeastern Mexico: Whole-Genome Sequencing With ExpansionHunter as a Key Diagnostic Tool

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Abstract

Dentatorubral-Pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder caused by a CAG trinucleotide-repeat expansion in the *ATN1* gene. DRPLA affects the dentate, red, pallid, and subthalamic nuclei. It is considered a form of spinocerebellar ataxia or progressive myoclonic epilepsy, usually characterized by ataxia, epilepsy, myoclonus, choreoathetosis, progressive cognitive decline, and neuropsychiatric symptoms. DRPLA is commonly classified into juvenile-onset disease (symptom onset before 20 years of age), which frequently presents with epilepsy and myoclonus, and adult-onset disease (symptom onset at 20 years of age or later), in which ataxia, choreoathetosis, and cognitive or neuropsychiatric manifestations are more prominent. In general, larger CAG repeat expansions are associated with an earlier age at onset, although considerable phenotypic variability exists. Molecular analysis is performed via repeat-primed PCR or Southern blot; both techniques are complex and not easily accessible. Particularly in Mexico, there are few laboratories that perform these tests. Therefore, whole-genome sequencing (WGS) using the ExpansionHunter (EH) methodology has shown good performance in detecting various classes of pathogenic tandem repeats relevant to human diseases, such as DRPLA, while also encompassing the analysis of differential diagnoses. We report a 24-year-old woman from Northeastern Mexico with behavioral and learning difficulties reported during childhood, epilepsy beginning at 16 years of age, nocturnal myoclonus, and progressive gait ataxia beginning at 20 years. Neurological examination revealed dyscalculia, dysarthria, ocular and dressing apraxia, left eye ptosis and esotropia, impaired coordination, dystonic movements, patellar hyperreflexia, resting tremor, gait instability, and dysdiadochokinesia. Brain magnetic resonance imaging (MRI) was reported to show cerebral white-matter signal abnormalities and generalized volume loss involving the cerebellum and brainstem. WGS data analyzed with EH identified a candidate repeat expansion in the pathogenic range of complete penetrance at *ATN1*. An orthogonal molecular assay was reported to identify alleles with 13 and 64 CAG repeats, respectively, supporting the molecular diagnosis of DRPLA. DRPLA is an infrequent polyglutamine disorder that should be considered in young patients with neurodevelopmental disorders, epilepsy, and progressive ataxia. The present case illustrates the feasibility of combining short-read WGS-based repeat-expansion screening with orthogonal molecular testing in the diagnostic evaluation of a patient with epilepsy, myoclonus, progressive ataxia, and cognitive/behavioral concerns. Therefore, the approach to these patients requires a multidisciplinary team and appropriate genetic counseling for confirmatory diagnosis, follow-up, prevention of possible complications, and recurrence risk management.

Categories: Neurology, Psychiatry, Genetics
Keywords: genetic counseling, leukoencephalopathies, progressive myoclonic epilepsies, trinucleotide repeat expansion, whole-genome sequencing

Introduction

Dentatorubral-pallidoluysian atrophy (DRPLA; OMIM #125370) is an autosomal dominant neurodegenerative disorder caused by an unstable expansion of CAG trinucleotide repeats in exon 5 of *ATN1* on chromosome 12p13.31. CAG encodes glutamine; therefore, an expanded repeat tract produces an abnormally long polyglutamine segment in the atrophin-1 (ATN1) protein. Polyglutamine disorders are characterized by progressive neuronal dysfunction, although their clinical manifestations and rates of progression vary substantially [1].

DRPLA is characterized by the combined degeneration of the dentatorubral and pallidoluysian systems. DRPLA can present with combinations of cerebellar ataxia, epilepsy, myoclonus, choreoathetosis or other

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involuntary movements, cognitive decline, and neuropsychiatric manifestations. Great intrafamilial variability and its clinical manifestations have been reported, as well as an anticipation effect directly related to the size of the CAG repeat expansion [1]. Juvenile-onset disease is conventionally defined by the onset of neurological manifestations before 20 years of age and is often epilepsy-predominant, whereas adult-onset disease more often presents with ataxia and choreiform movements. Longer CAG expansions are generally associated with earlier onset and greater severity. Intergenerational instability may lead to genetic anticipation, particularly with paternal transmission. Additionally, the imaging findings from brain magnetic resonance imaging report cerebellar and brainstem atrophy and possibly white matter lesions [2,3].

Molecular diagnosis requires demonstration of a pathogenic *ATN1* CAG-repeat expansion. Diagnosing DRPLA in patients is challenging as traditional methods of identifying these expansions are often laborious and locus-specific, and they cannot accurately determine long repeat expansions and require a high level of diagnostic suspicion. The main tests used are repeat-primed polymerase chain reaction (PCR) and Southern blotting [4]. Therefore, whole-genome sequencing (WGS) is increasingly being used as a first-line test for other genetic disorders caused by repeat expansions, as it has demonstrated high sensitivity and specificity [5]. This application of WGS has also been made possible by the advancement and development of bioinformatics technology, such as the ExpansionHunter (EH) method, which is a genome-wide, catalog-free screening method that can flag candidate repeat expansions from short-read sequencing data and is computationally efficient [6].

Here, we describe a woman from Northeastern Mexico with adolescent-onset epilepsy, nocturnal myoclonus, progressive gait ataxia, cognitive/learning difficulties, and a reported *ATN1* expansion identified through WGS-based screening and subsequent molecular testing. The aim is to highlight clinical features that may prompt consideration of DRPLA.

Case Presentation

A 24-year-old right-handed woman from and residing in Nuevo León, Mexico, was evaluated for epilepsy and progressive gait disturbance. She had completed secondary education and was unemployed at the time of assessment. According to family report, her father died at 57 years of age from a gastrointestinal stromal tumor. Relatives described him as having paranoid and obsessive behavioral traits, including suspiciousness, impulsivity, and excessive preoccupation with work; he had no documented neurological examination or genetic testing. One sister, aged 31 years, was reported to have depression, and another sister, aged 21 years, was reported to have borderline personality disorder (Figure *1*).

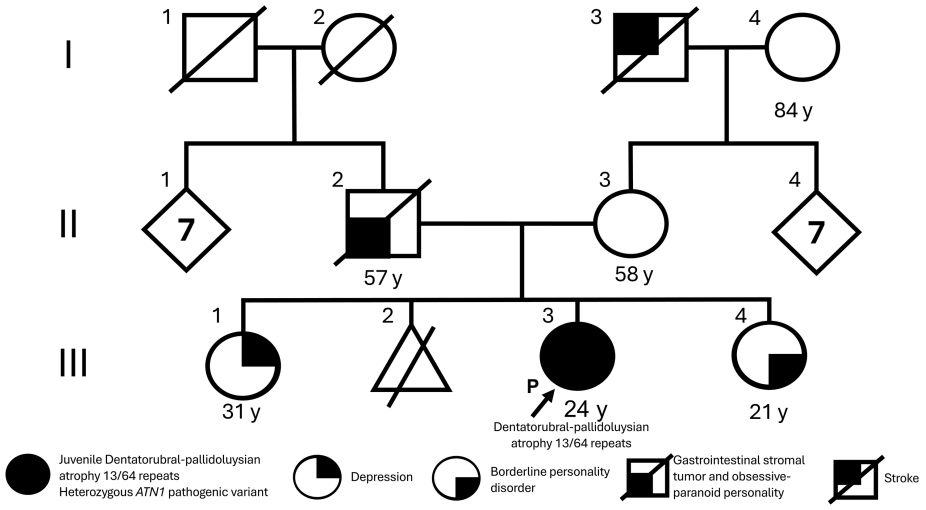


FIGURE 1: Pedigree of the patient.

The generations are described with Roman numerals (I, II, III) and the individuals with Arabic numerals (1, 2, 3). The squares represent men, the circles represent women, the triangle represents an abortion product, and the diamonds represent a group of individuals involving both sexes, with the number inside each diamond indicating the number of individuals it represents. The diagonal line represents that the individual has passed away. The reported patient is individual III3, who was diagnosed with DRPLA with a normal allele of 13 repeats and an altered allele with 64 repeats.

DRPLA: dentatorubral-pallidoluysian atrophy

The patient was the product of the third pregnancy. The source history reports prenatal care and maternal folic acid and hematinic supplementation, no recognized prenatal complications, and cesarean delivery at 38

weeks because of cephalopelvic disproportion. Birth weight was reported as 3,800 g, birth length of 58 cm, and APGAR scores were 8 at 1 minute and 9 at 5 minutes [7]. She was discharged together with her mother without reported complications. There was no reported exposure to wood smoke or known teratogens, and the patient denied alcohol or tobacco consumption, illicit drug use, previous surgical procedures, blood transfusions, significant traumatic events, or adverse drug reactions.

The first behavioral and cognitive manifestations were noted at four years of age, when she began to exhibit fear of making mistakes while performing tasks, low frustration tolerance, and perfectionistic personality traits. Epilepsy was diagnosed at 16 years of age. Events reported included generalized tonic-clonic seizures lasting approximately 3 to 4 minutes, followed by approximately 15 minutes of tiredness and hunger. The family reported approximately four to five seizure episodes per year and also described focal seizures with gelastic semiology. Nocturnal myoclonus was also observed by family members. At the time of evaluation, her antiseizure treatment consisted of levetiracetam 1000 mg every 12 hours, valproate 900 mg every 12 hours, and lamotrigine 50 mg every 12 hours; her last reported seizure occurred in March 2026.

Neuropsychological testing (The WAIS-IV Intelligence Test (Wechsler Adult Intelligence Scale-IV), Wechsler Memory Scale-IV subtest, Subtest of the Barcelona Test, adapted for age, Rey-Osterrieth Complex Figure Copy Test, d2 attention test, Stroop color-word test, Trail Making Test, Wisconsin Card Sorting Test PROLEC-SE-R reading test), performed in 2018 reportedly yielded a full-scale intelligence quotient (IQ) of 41 and described dyslexia associated with visuospatial deficits, dysgraphia associated with impaired phonological analysis, dyscalculia associated with visuospatial deficits, and poor task execution.

On physical examination, the patient was awake, oriented to person, and inattentive. Speech was dysarthric with a scanning quality. Cognitive/bedside findings included impaired working memory, dyscalculia, and dressing apraxia. Cranial nerve examination documented left ptosis, esotropia, and dysmetric saccades. Motor examination showed altered axial tone and globally reduced strength, graded 4/5 on the Medical Research Council (MRC) scale [8]. Plantar responses were bilaterally extensor. Deep tendon reflexes were 2+ at the triceps, biceps, and brachioradialis; 3+ at the patellar tendons; and 4+ at the Achilles tendons. Exteroceptive sensation was reported as preserved. Dystonic movements and a resting tremor involving the neck and right arm were observed. Gait was wide-based and ataxic, with postural instability, reduced arm swing, and freezing during turns. Dysdiadochokinesia and right-sided finger-to-nose dysmetria were reported. There was not observed nystagmus or atavistic reflexes (glabellar tap, palmomental, snout and sucking reflexes).

Brain magnetic resonance imaging (MRI) performed in June 2026 was reported to show symmetric, patchy T2/FLAIR hyperintensities in the centrum semiovale and white matter adjacent to the occipital horns of both lateral ventricles, with generalized cortical and subcortical volume loss and cerebellar and brainstem atrophy, including reduced cerebellar and midbrain volume (Figure *2*).

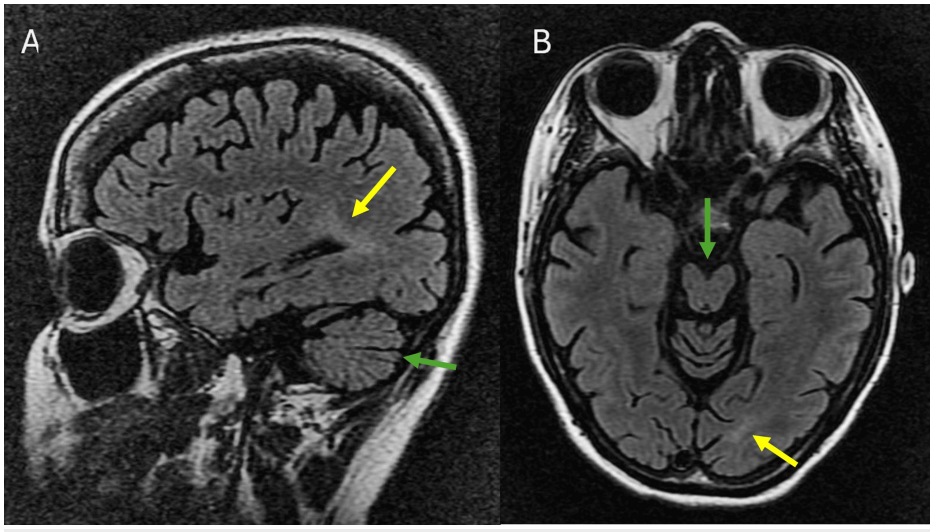


FIGURE 2: MRI of the brain in T2/FLAIR sequence.

(A) Sagittal section showing hyperintensity in the occipital recess of the left lateral ventricle, generalized cortical parenchyma reduction (yellow arrow), and reduction in cerebellar volume (green arrow). (B) Axial image showing hyperintensity in the occipital recess of the left lateral ventricle (yellow arrow), generalized cortical parenchyma reduction, and reduced midbrain volume (green arrow).

MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery

The videoelectroencephalogram performed in June 2026 reported basal activity consisting of generalized theta rhythm, sparse anterior beta rhythm, and impaired integration of amplitude and frequency gradients in the anteroposterior direction (Figure *3*).

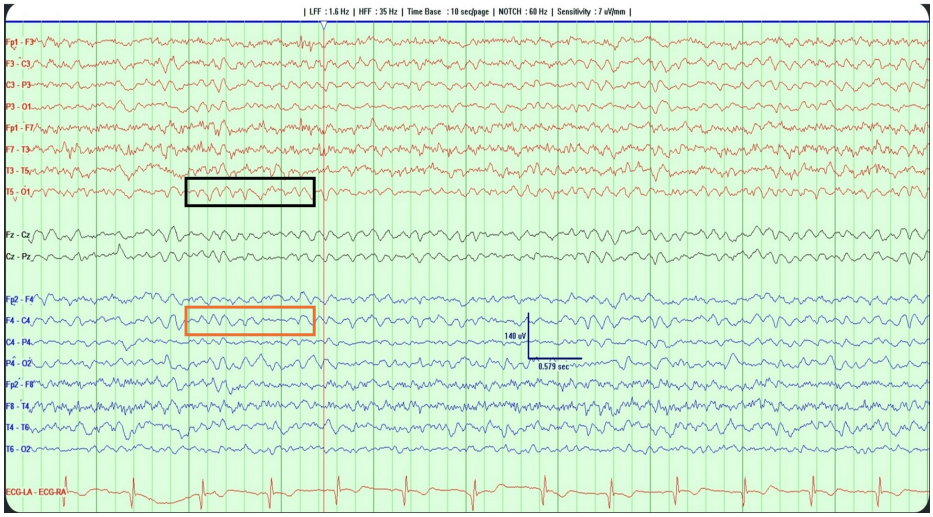


FIGURE 3: Electroencephalogram of the patient.

The tracing shows generalized theta activity (black rectangle) and sparse anterior beta activity (orange rectangle), with impaired integration of amplitude and frequency gradients in the anteroposterior direction.

WGS was performed using genomic DNA that underwent enzymatic fragmentation and library preparation. Paired-end sequencing was carried out on an Illumina Platform, achieving a mean sequencing depth of ~30X. Sequence data were subsequently processed using a bioinformatics pipeline incorporating Illumina's DRAGEN algorithm. The reads were aligned to the Genome Reference Consortium Human Build 37 (GRCh37/hg19) reference genome, as well as to the revised Cambridge Reference Sequence (rCRS) for human mitochondrial DNA (NC_012920), and variants were classified according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines. Also, WGS data were analyzed with the EH algorithm, which identified a candidate repeat-expansion signal at *ATN1*. An orthogonal repeat-primed PCR assay (PCR and capillary electrophoresis to detect repetitive nucleotide motif(s), reference sequence for ATN1:NM_001007026.1) was reported to identify two *ATN1* alleles containing 13 and 64 CAG repeats, respectively, consistent with a heterozygous pathogenic expansion and supporting DRPLA. Thus, the combination of a reported 64-CAG *ATN1* allele and the clinical history of adolescent-onset epilepsy, myoclonus, progressive ataxia, movement abnormalities, and cognitive concerns supports the diagnosis of juvenile-onset DRPLA. The timeline of diagnosis is shown in Figure *4*.

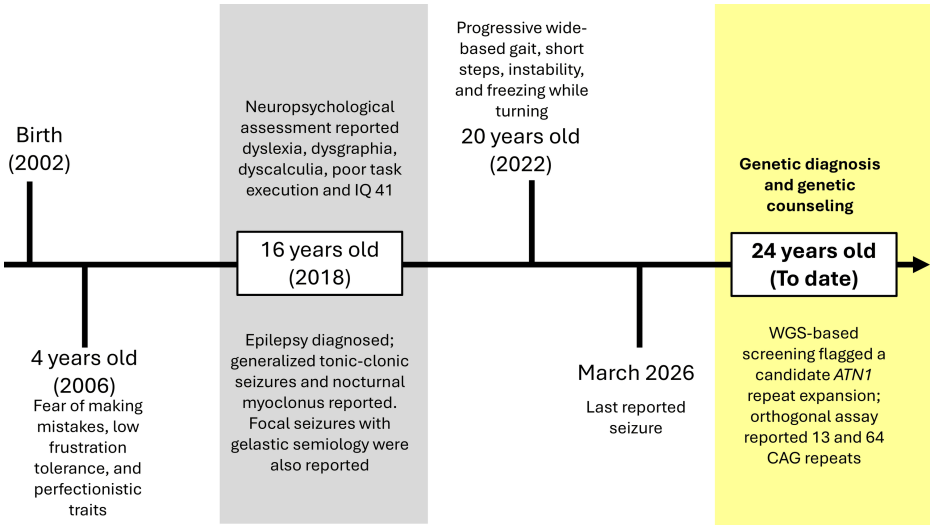


FIGURE 4: Clinical timeline of the patient.

The timeline summarizes the patient's clinical course; events are presented according to the age or date documented in the clinical record. The figure was created using Microsoft PowerPoint (Microsoft Corporation; Redmond, Washington, USA).

WGS: whole-genome sequencing

Repeat neuropsychological testing is currently pending as part of the patient's multidisciplinary follow-up. The patient is currently undergoing further evaluation for suspected autism spectrum disorder. Additional evaluations, including neuro-ophthalmological assessment and polysomnography, were requested and remain pending.

Discussion

This report describes a woman with a molecularly supported diagnosis of DRPLA whose clinical history includes epilepsy beginning at 16 years, reported nocturnal myoclonus, progressive gait ataxia beginning at 20 years, dystonic movements, tremor, cognitive/learning difficulties, and MRI findings reported to include cerebellar and brainstem volume loss and cerebral white-matter signal abnormalities. The most decisive diagnostic evidence is the reported heterozygous *ATN1* expansion of 64 CAG repeats.

CAG trinucleotide repeat disorders include neurodegenerative disorders known as polyglutamine diseases (polyQ) or polyglutaminopathy, caused by expansions of CAG repeats in the coding regions of disease-causing genes. The nine known polyQ diseases include Huntington's disease (HD), DRPLA, spinal and bulbar muscular atrophy (SBMA), and six spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17) [9]. The involvement of pathological molecular attributes has been described in almost all of them, including protein aggregation, proteolytic cleavage, neuronal dysfunction, transcriptional dysregulation, autophagy impairment, and mitochondrial dysfunction. Although there are animal models of polyQ diseases that help to understand their pathogenesis and access disease-modifying therapies, there is no cure or prevention for these diseases, and only symptomatic treatments are available [10].

Particularly, DRPLA is the result of an unstable expansion of CAG trinucleotide repeats in exon 5 of the *ATN1* gene that encodes for the Atrophin-1 protein. The number of CAG trinucleotide repeats typically ranges between 6 and 34 repeats. When patients present with ⩾ 48 CAG trinucleotide repeats, complete penetrance occurs (which describes the proportion of individuals carrying a disease-associated allele who develop clinical manifestations), whereas alleles with between 35 and 47 CAG trinucleotide repeats have incomplete penetrance and are generally associated with a milder clinical phenotype. Moreover, DRPLA exhibits a genetic anticipation phenomenon with paternal transmission, presenting a more severe and earlier phenotype in each subsequent generation [11].

Most reported cases of DRPLA come from the Asian population. In Japan, the prevalence of DRPLA is 0.2-0.7/100,000 people and is comparable to that of Huntington's disease (HD; prevalence of 0.4-0.5/100,000), which is the most common repeat expansion disorder in North America and Europe. The prevalence of HD in North America is 8.9/100,000. In contrast, DRPLA is extremely rare in Western Europe and North America, with several dozen patients described in the literature and confirmed in an ongoing natural history study [12].

In fact, in Portuguese families diagnosed with DRPLA, it was shown that they shared a common haplotype of Asian origin, which was more frequent in Japanese alleles and rare in Europeans, suggesting a founder effect [13,14]. However, because there are few cases described related to DRPLA, the characterization of Asian haplotypes for DRPLA in the Mexican population has not been reported to date.

The *ATN1* gene consists of 10 exons that code for the Atrophin-1 (ATN-1) protein, composed of 1,190 amino acids with a molecular weight of 125 kDa. The polyglutamine (polyQ) tract is located in the central region of the protein, encoded by exon 5. The expression of *ATN1* is generally low, but it is mostly expressed in the brain, particularly in the amygdala, caudate nucleus, hippocampus, and hypothalamus. It is also proposed that it might be of importance for the early development of the central nervous system, because higher expression of *ATN1* is found in the fetal brain [15].

DRPLA occurs when there is an expansion in the number of repeats of the CAG trinucleotide in the *ATN1* gene, resulting in an abnormally expanded chain of glutamine residues (encoded by the CAG codon) in the ATN1 protein, known as polyQ, causing this protein to aggregate, generating cytotoxicity, and leading to neurodegeneration of the dentatorubral-pallidoluysian systems [16]. It has also been described that in DRPLA, protein-protein interactions are altered, in which the amplified polyQ bundles play a crucial role in the dysregulation of gene expression and neuronal death [17].

It should be mentioned that de novo mutations (mainly missense or deletions) in exon 7 of the *ATN1* gene, which encodes the histidine repeat motif (HX), cause a condition called CHEDDA (congenital hypotonia, epilepsy, developmental delay, and finger anomalies), which is a different entity from DRPLA, caused by the expansion of CAG trinucleotides in exon 5 of the *ATN1* gene [15,18,19].

The length of the CAG trinucleotide repeat expansion in DRPLA has a close correlation with the age of onset and functional decline, such that longer repeats are associated with an earlier onset and a more severe disease phenotype [9]. The average age of onset of DRPLA is 31 years and is dependent on the size of the repeat expansion. Alleles with ≥48 repeats cause clinical symptoms. While the presence of >65 repeats often manifests with juvenile-onset progressive myoclonic epilepsy (PME), repeats <65 are associated with a phenotype without PME, primarily characterized by ataxia and cognitive impairments [20]. Our patient, harboring an *ATN1* allele with 64 CAG repeats, presented with cognitive impairment, epilepsy, ataxia, dystonia, tremor, and white matter abnormalities, while intellectual disability and autism spectrum disorder remain under diagnostic evaluation.

Within their approach, it has been demonstrated that magnetic resonance imaging can identify the presence of high-intensity signals in T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) sequences located in the cerebral white matter, brainstem, and thalamus, as well as atrophy of the brain, brainstem, and cerebellum [21]. The reported patient presented white matter lesions in the semioval centers, occipital recesses of the lateral ventricles, and atrophy of the midbrain and cerebellum (Figure *2*). Although the neuroimaging findings are compatible with DRPLA, they are not specific to the disease and other conditions associated with cerebral white-matter abnormalities must be considered, including leukodystrophies and metabolic or mitochondrial disorders. Furthermore, a combination of symptoms such as progressive ataxia, myoclonus, epilepsy and cognitive or behavioral abnormalities can lead to a diagnosis of conditions such as Huntington's disease, Huntington's disease-like disorders, spinocerebellar ataxias, progressive myoclonic epilepsy, neuronal ceroid lipofuscinosis, Wilson's disease and certain acquired or autoimmune neurological conditions [22].

Likewise, white matter lesions, such as leukodystrophies, can present with psychiatric disorders such as depression, anxiety disorders, personality changes, and mood lability throughout the course of the disease. Approximately 10% of patients with DRPLA develop schizophrenia-like psychosis, which may include delusions and hallucinations [23]. In this regard, the reported patient has a family history of psychiatric disorders, mainly from the father, who is hypothesized to have had the expansion, but segregation could not be performed due to his death (Figure *1*, individual II2).

Traditionally, it has been difficult to detect repeat expansions using NGS data, as for this methodology, DNA is divided into short fragments or reads that range from 50 to 300 bases before being sequenced. Therefore, repetitive regions longer than the read length cannot be accurately analyzed. However, a bioinformatics tool called EH has been developed, which estimates repeat sizes at known short tandem repeat (STR) *loci* using exome or genome sequencing data. EH has proven to be capable of detecting expanded and non-expanded alleles in 13 *loci* of the most prevalent repeat expansion disorders with high specificity (100%) and sensitivity (99.1%) [6,24].

EH is a novel method for conducting a genome-wide search for expansions of repetitive sequence regions. To address the limitations of existing approaches, EH scans the existing alignments of short reads from one or multiple sequencing libraries to identify changes in nucleotide composition within expanded repeats and is applicable to both short and long motifs. Moreover, EH is computationally efficient because it does not realign the reads and can analyze a single 30 to 40x WGS sample in approximately 30 minutes to two hours [6]. EH is currently the reference tool for genotyping tandem repeat sequences known in pathogenic *loci*, due

to its precision and computational efficiency, genomic-level approaches, and the ability to generate important new candidate *loci* [25].

Currently, there are also other alternatives to detect STR expansions with greater precision through long-read sequencing technologies, such as Oxford Nanopore Technology (ONT) and Pacific Biosciences (PacBio) single-molecule real-time (SMRT) sequencing. These technologies allow researchers to obtain single reads of more than 10 kb, sometimes reaching up to 1-2 Mb. However, these methodologies require specific DNA extraction processing from fresh blood samples or living cells to obtain good results [26]. However, in the clinical aspect, we face the limitations of the availability of these technologies in our country.

Regarding the progression of the disease, the symptoms lead to progressive motor and swallowing functional disorders, resulting in a decrease in activities of daily living and difficulties with oral ingestion. It is postulated that patients with juvenile onset often experience a faster progression than patients with adult onset [27].

Currently, no specific treatment has been established for DRPLA; management is exclusively symptomatic and multidisciplinary [11]. Management includes rehabilitation and physiotherapy (balance, gait, and strengthening), occupational therapy to optimize activities of daily living; adaptive devices (canes, walkers, motorized chairs); weight control and home adaptations to prevent falls. Pharmacological treatment for the manifestations of choreoathetosis and dystonia with tetrabenazine, risperidone, bromazepam, and gabapentin. For dysphagia problems, use swallowing therapy programs and education to mitigate the risk of aspiration. In the nutritional aspect, a nutritional evaluation is necessary, vitamin supplementation as needed, and avoiding obesity. For psychiatric disorders, quetiapine can be useful for psychosis, and it is important to consider cognitive-behavioral therapy. Eventually, it is necessary to consider continuous assessment, palliative care, or home nursing [28].

Given that DRPLA shares a pathophysiological mechanism with HD, antisense oligonucleotides (ASO) targeting *ATN1* mRNA, protein aggregation inhibitors, and small molecules that induce contraction of the CAG repeat (such as naphthyridine-azaquinolone, effective in a mouse model of DRPLA) are being investigated. These strategies are still in the preclinical phase or in early trials for related polyQ disorders, without regulatory approval for DRPLA [16,29,30].

Thus, timely diagnosis and identification of people with rare diseases, such as DRPLA, represents a step forward toward the visibility of these conditions. Having a definitive diagnosis provides guidance toward the search for targeted management and ends the diagnostic odyssey for patients who have spent years visiting different specialists. Unfortunately, access to genetic studies in Latin America presents significant challenges, mainly due to limited access to tests for the population across countries and regions, as well as the availability of financial resources for their implementation. It is estimated that nearly 75% of individuals affected by rare diseases remain undiagnosed in Latin America, highlighting the urgent need to improve access to comprehensive genetic services and the reporting of these pathologies in current medical literature [31].

This case report has limitations. Family segregation analysis could not be performed because the patient's father had died before genetic testing could be undertaken, while genetic testing of other relatives was not feasible due to financial constraints. Consequently, the parental origin of the expanded *ATN1* allele remains unknown, and neither familial transmission nor genetic anticipation could be established. Although previous neuropsychological testing documented significant cognitive impairment, further assessment is required to characterize adaptive functioning, longitudinal cognitive changes, and the possibility of coexisting intellectual disability or autism spectrum disorder, both of which remain under diagnostic evaluation. Furthermore, access to specialized healthcare services and advanced diagnostic testing remains challenging in the patient's socioeconomic context. Financial barriers and limited accessibility to specialized multidisciplinary care have delayed the completion of additional evaluations, including repeat neuropsychological testing, neuro-ophthalmological assessment, and polysomnography. These circumstances have also limited the availability of comprehensive longitudinal follow-up.

Conclusions

Reports of DRPLA in Mexican patients are limited, both due to clinical suspicion and the availability of confirmatory studies in the general population. In this patient, epilepsy beginning during adolescence, myoclonus, progressive ataxia, movement abnormalities, cognitive concerns, and a reported heterozygous *ATN1* allele containing 64 CAG repeats support a diagnosis of juvenile-onset DRPLA. Juvenile DRPLA is a very rare polyglutamine disorder outside of the Japanese population that should be considered in young patients with neurodevelopmental disorders, epilepsy, and progressive ataxia. The diagnosis through molecular studies allows for the exclusion of hereditary leukodystrophies, spinocerebellar ataxias, and progressive epilepsies with similar presentations, guiding symptomatic management and offering genetic counseling to the family. Also, the case illustrates how WGS with EH analysis is a valuable tool for diagnosing repeat expansion diseases for subsequent locus-specific molecular confirmation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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