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Case Report

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Ocular Motor and Vestibular Profile in Adult-Onset Cerebellar Ataxia Associated With a Homozygous *ERCC4* Variant: A Case Report and Systematic Review

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Running title: Ocular Motor Profile in *ERCC4*-Related Cerebellar Ataxia

Keywords: *ERCC4*; nucleotide excision repair; cerebellar ataxia; videonystagmography; saccadic intrusions; vestibular function; sensorineural hearing loss; xeroderma pigmentosum complementation group F; systematic review.

Abstract

Background: Biallelic *ERCC4* variants cause nucleotide excision repair (NER) disorders, including adult-onset multisystem neurodegeneration. We report the ocular motor, vestibular, and audiological profile of a patient with a homozygous *ERCC4* variant and systematically review previously reported adult patients.

Case Presentation: A 58-year-old man presented with a 13-year history of slowly progressive ataxia, dysarthria, memory decline, and reduced hearing. Examination showed a pancerebellar syndrome, brisk tendon reflexes, mild chorea, and diffuse skin hyperpigmentation without photosensitivity. Videonystagmography revealed complex saccadic intrusions, head-shaking–

induced vertical nystagmus, saccadic dysmetria with intermittent slowing of vertical saccades, and reduced vertical smooth pursuit and optokinetic gains. Video head impulse testing was normal in all six semicircular canals, whereas audiometry showed bilateral high-frequency sensorineural hearing loss. Cognitive assessment revealed global mnestic deterioration, and MRI showed severe cerebellar atrophy with mild brainstem and global cerebral atrophy. Whole-exome sequencing identified the homozygous *ERCC4* variant c.2395C>T, p.(Arg799Trp).

Systematic Review: A PRISMA-guided search of PubMed/MEDLINE, Scopus, and Web of Science identified ten reports describing 22 adults. Ataxia, chorea, and cognitive impairment were almost universal, and an ataxia-predominant phenotype was most common. Ocular motor abnormalities, mainly saccadic pursuit and saccadic dysmetria, had been described mostly qualitatively, whereas saccadic intrusions, optokinetic abnormalities, and head-shaking nystagmus had not been reported. Hearing loss was reported in 12 patients, but vestibular function had been tested in only one, with normal results.

Discussion: *ERCC4*-related neurodegeneration is a heterogeneous multisystem disorder. Central ocular motor dysfunction, sensorineural hearing loss, and preserved peripheral vestibular function may support the diagnosis, and NER genes should be considered in adults with ataxia, chorea, and cognitive decline, even without photosensitivity.

1 Introduction

The *ERCC4* gene encodes the XPF endonuclease, an essential component of the nucleotide excision repair (NER) pathway that is also required for the repair of DNA interstrand crosslinks. Biallelic pathogenic *ERCC4* variants cause several autosomal recessive disorders, including xeroderma pigmentosum complementation group F (XP-F), xeroderma pigmentosum type F/Cockayne syndrome, Fanconi anaemia complementation group Q (FANCQ), and XFE progeroid syndrome (1, 2).

NER disorders are clinically heterogeneous. Classical features include photosensitivity and an increased risk of skin cancer, with developmental delay and early-onset neurodegeneration in some phenotypes. Adult-onset neurodegeneration in autosomal recessive NER disorders (NERDND) has been recognised as a distinct and probably underdiagnosed multisystem disorder, combining progressive ataxia and dementia with chorea, neuropathy, spasticity, profound global brain atrophy, and variable, often minimal, skin involvement (3).

Subsequent reports described *ERCC4*-related cerebellar ataxia with chorea, dysarthria, cognitive decline, and bilateral hearing loss (4), late-onset chorea mimicking Huntington's disease (5, 6), and a very slowly progressive phenotype with cerebellar and brainstem atrophy and only very mild skin involvement (7). Ocular motor abnormalities, such as saccadic pursuit, hypometric saccades, and antisaccade errors, have been described mostly qualitatively, and quantitative video-oculographic, vestibular, and audiological data remain scarce (4, 5, 7). Video-oculography can objectively characterise cerebellar and brainstem ocular motor dysfunction, including saccadic intrusions, nystagmus, and deficits of saccades and smooth pursuit (8), and, combined with video head impulse testing, helps distinguish central from peripheral vestibular involvement in late-onset cerebellar ataxias (9).

We report a patient with genetically confirmed *ERCC4*-related neurodegeneration presenting as a complex multisystem disorder. The novelty of this report lies in the comprehensive clinical, genetic, ocular motor, vestibular, and audiological assessment, with particular focus on the ocular motor and audiovestibular profile. To place these findings in context, we systematically reviewed previously reported adult patients with *ERCC4*-related neurodegeneration.

2 Case Presentation

A 58-year-old man was admitted to our tertiary neurological centre for evaluation of a gait and balance disorder that had progressed slowly over approximately 13 years. He reported worsening coordination, chronic dizziness, long-standing memory decline, and reduced

hearing; over the preceding years, these symptoms had been attributed to non-specific, vascular, or cervicogenic causes. His medical history included degenerative spine disease with L3/L4 transforaminal lumbar interbody fusion and multilevel cervical osteochondrosis (C3–C7) with spinal canal stenosis. Before admission, he was taking vinpocetine and thiethylperazine. He had completed secondary education, had worked as a manual labourer, and reported no alcohol use. His mother died of acute leukaemia at the age of 42 years. The family history was otherwise negative for ataxia, dementia, and hearing loss. No parental consanguinity was known, but both parental families originated from the same small village in northern Slovakia.

Neurological examination revealed a symmetric pancerebellar syndrome with bilateral dysmetria, dystaxia, and dysdiadochokinesia of the upper limbs (Supplementary Video 1), bilateral dysmetria and dystaxia of the lower limbs (Supplementary Video 2), and ataxic gait with marked impairment of tandem gait (Supplementary Video 3). Truncal ataxia increased with feet together, Romberg's sign was present, and the head tended to tilt to the right. Mild cerebellar dysarthria was present, and the Scale for the Assessment and Rating of Ataxia (SARA) score was 14–15/40. Muscle tone and strength were normal, tendon reflexes were symmetrically brisk without pathological reflexes, and tactile sensation was preserved. Mild generalised chorea was present without hypokinesia (Supplementary Video 1). Frontal release signs were present. On bedside examination, there was no spontaneous or gaze-evoked nystagmus, saccades were mildly hypometric, and the vestibulo-ocular reflex (VOR) was preserved. Antisaccades, assessed clinically in 10 trials, showed fewer than 20% errors (fewer than 2 of 10) and were considered normal. Fundoscopy showed no papilloedema.

Brain MRI showed severe symmetric cerebellar atrophy, mild brainstem atrophy with subnormal pontine volume, and mild global cerebral atrophy (grade 1 on the global cortical atrophy scale) (Figure 1); serial MRI examinations since 2012 had documented progression of the cerebellar atrophy.

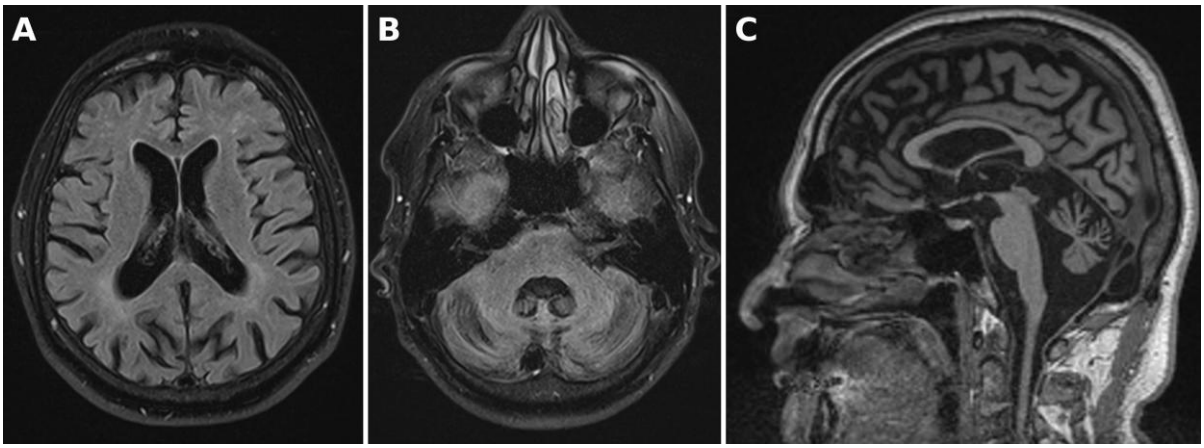


Figure 1. Brain MRI. (A) Axial fluid-attenuated inversion recovery (FLAIR) image at the level of the lateral ventricles showing global cerebral atrophy with widened cortical sulci and enlarged lateral ventricles. (B) Axial FLAIR image of the posterior fossa and (C) midsagittal T1-weighted image showing severe cerebellar atrophy.

Videonystagmography (VNG) showed a central pattern of ocular motor dysfunction. During fixation, saccadic intrusions exceeded the physiological range and comprised square-wave jerks, macro square-wave jerks, monophasic saccadic pulses, and staircase saccadic oscillations, without spontaneous nystagmus (Figure 2A; Supplementary Video 4). Eccentric gaze holding showed only occasional nystagmoid jerks or saccadic oscillations in the horizontal traces, without sustained gaze-evoked nystagmus (Figure 2B). Head shaking provoked vertical pendular oscillations/nystagmus (slow-phase velocity 1.9°/s), followed after a few seconds by saccadic oscillations (Figure 2C).

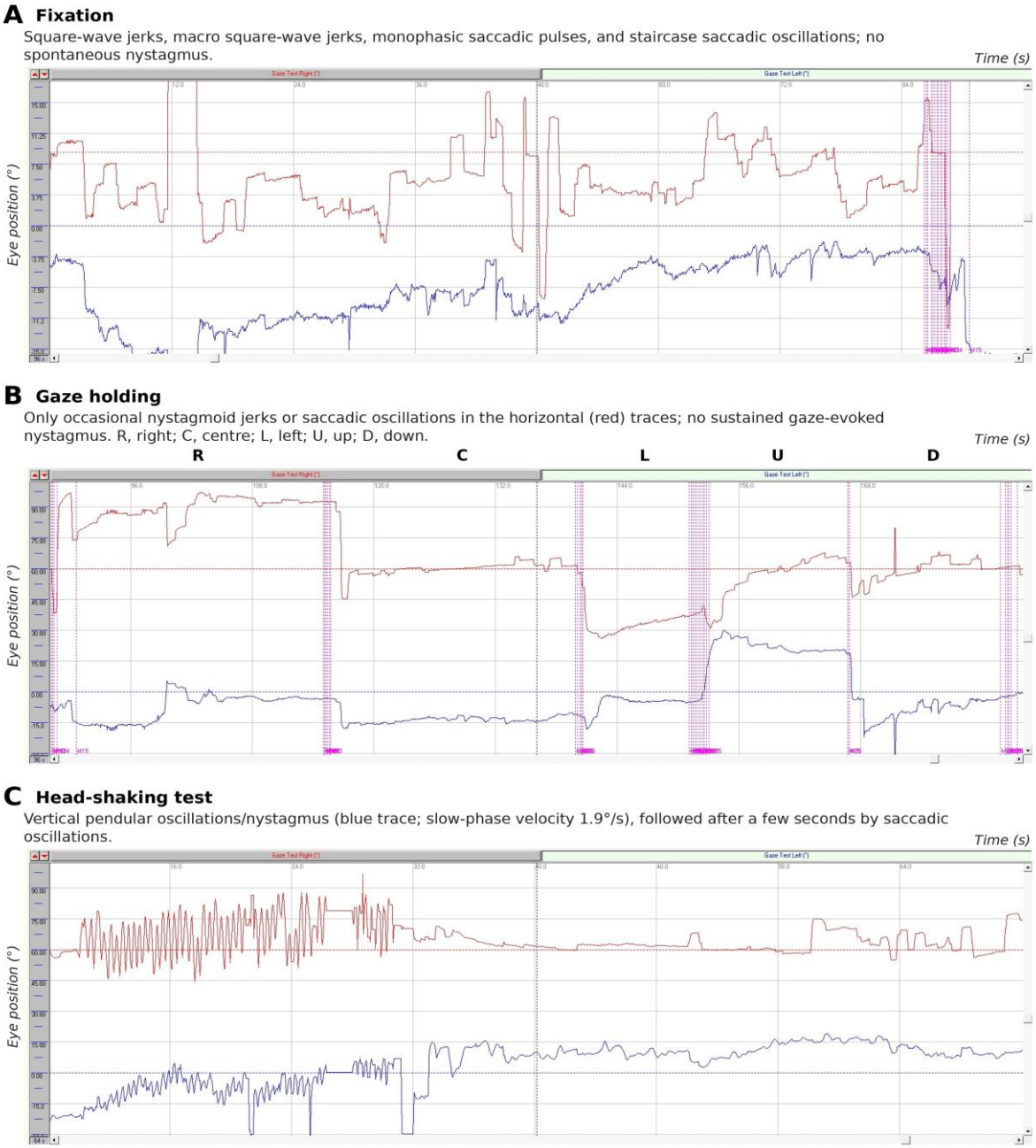
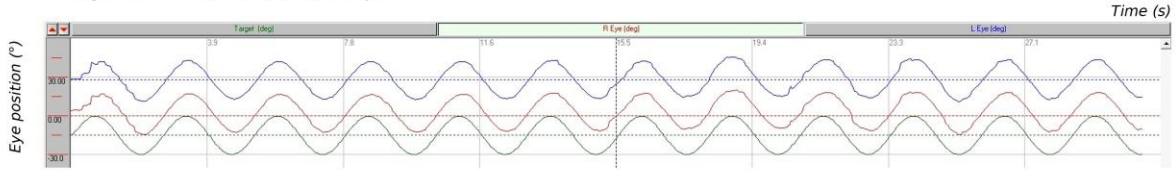


Figure 2. Videonystagmography during fixation, gaze holding, and head shaking. (A) Fixation of a central target showing excessive, heterogeneous saccadic intrusions without spontaneous nystagmus. (B) Gaze holding in right (R), central (C), left (L), upward (U), and downward (D) positions, with occasional nystagmoid jerks or saccadic oscillations in the horizontal traces and no sustained gaze-evoked nystagmus. (C) Head-shaking test showing vertical pendular oscillations/nystagmus (slow-phase velocity 1.9°/s) followed by saccadic oscillations. Red trace, horizontal eye position; blue trace, vertical eye position. Time is shown in seconds and position in degrees.

Smooth pursuit, saccades, and optokinetic nystagmus (OKN) were recorded binocularly. Smooth pursuit (sinusoidal target, amplitude 30°, 0.4 Hz) showed preserved horizontal gain (0.87 rightward, 0.84 leftward) and slightly reduced vertical gain (0.57 upward, 0.55 downward), with identical values in both eyes (Figure 3A, B). Saccades (target steps of 30°, 0.4 Hz) showed intermittent dysmetria, more pronounced in the vertical plane, where intermittent slowing was also present (Figure 3C, D). Latency, peak velocity, and precision, calculated automatically by the VNG software (right/left eye), were 190/173 ms, 342/355°/s, and 88%/89% for rightward; 217/193 ms, 368/334°/s, and 86%/84% for leftward; 198/175 ms, 296/274°/s, and 87%/84% for upward; and 202/184 ms, 189/203°/s, and 97%/95% for downward saccades. OKN gains (right/left eye) were reduced, more markedly with vertical stimulation: 0.70/0.95 leftward (20°/s; Figure 3E), 0.91/0.79 rightward (25°/s; Figure 3F), 0.57/0.70 upward (20°/s; Figure 3G), and 0.23/0.38 downward (20°/s; Figure 3H).

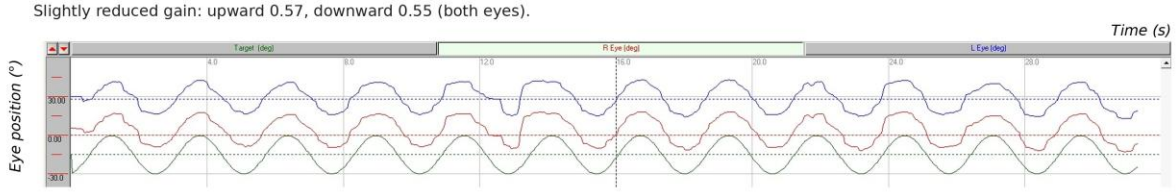
A Horizontal smooth pursuit (sinusoidal target, amplitude 30°, 0.4 Hz)

Gain: rightward 0.87, leftward 0.84 (both eyes).



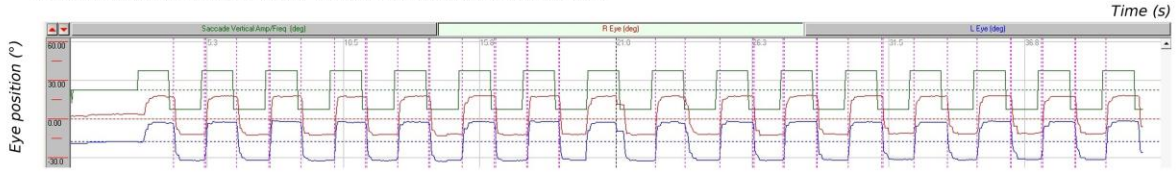
B Vertical smooth pursuit (sinusoidal target, amplitude 30°, 0.4 Hz)

Slightly reduced gain: upward 0.57, downward 0.55 (both eyes).



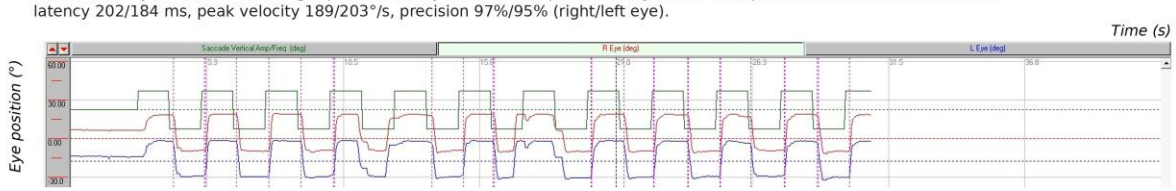
C Horizontal saccades (target steps 30°, 0.4 Hz)

Intermittent dysmetria. Rightward: latency 190/173 ms, peak velocity 342/355°/s, precision 88%/89%. Leftward: latency 217/193 ms, peak velocity 368/334°/s, precision 86%/84% (right/left eye).



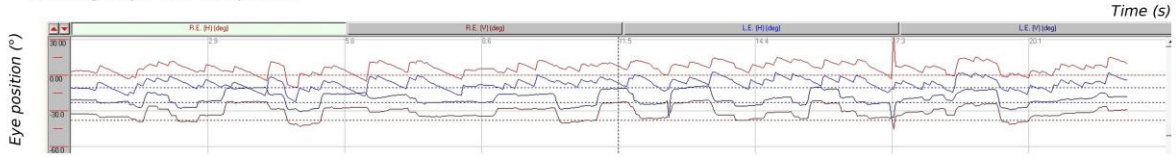
D Vertical saccades (target steps 30°, 0.4 Hz)

Intermittent dysmetria and slowing. Upward: latency 198/175 ms, peak velocity 296/274°/s, precision 87%/84%. Downward: latency 202/184 ms, peak velocity 189/203°/s, precision 97%/95% (right/left eye).



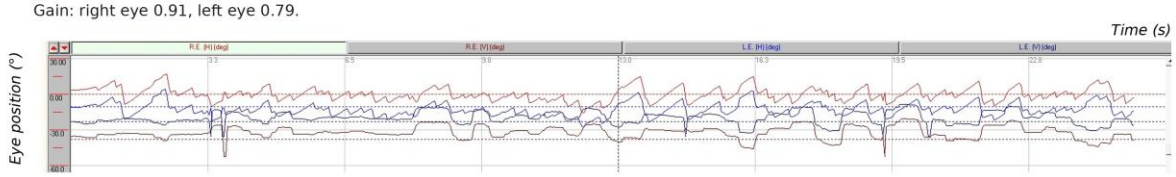
E Optokinetic nystagmus, leftward stimulus 20°/s

Gain: right eye 0.70, left eye 0.95.



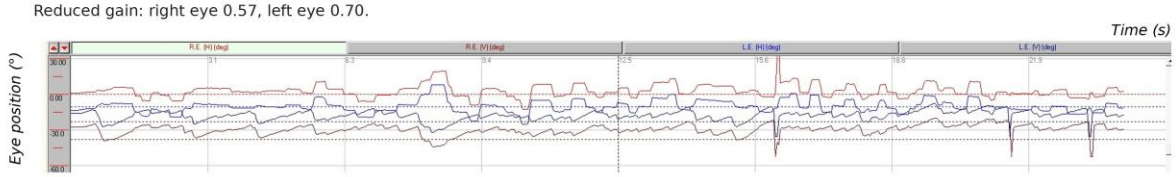
F Optokinetic nystagmus, rightward stimulus 25°/s

Gain: right eye 0.91, left eye 0.79.



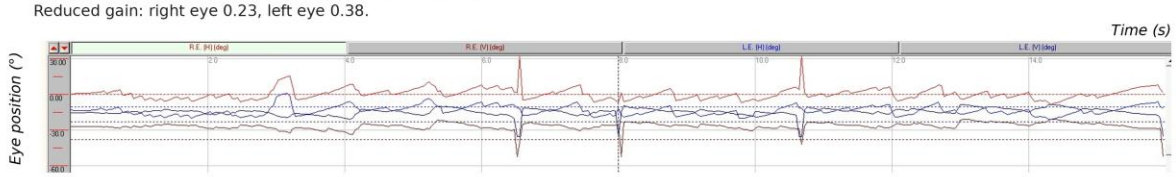
G Optokinetic nystagmus, upward stimulus 20°/s

Reduced gain: right eye 0.57, left eye 0.70.



H Optokinetic nystagmus, downward stimulus 20°/s

Reduced gain: right eye 0.23, left eye 0.38.



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Figure 3. Videonystagmography of smooth pursuit, saccades, and optokinetic nystagmus (binocular recording). (A) Horizontal and (B) vertical smooth pursuit (sinusoidal target, amplitude 30°, 0.4 Hz). (C) Horizontal and (D) vertical saccades (target steps of 30°, 0.4 Hz) showing intermittent dysmetria and, in the vertical plane, intermittent slowing. (E–H) Optokinetic nystagmus with leftward (E, 20°/s), rightward (F, 25°/s), upward (G, 20°/s), and downward (H, 20°/s) stimulation. Gain, latency, peak velocity, and precision (automatic software analysis) are given above each panel. Time is shown in seconds and position in degrees.

Video head impulse testing (vHIT) was normal in all six semicircular canals, with mean VOR gains of 1.04 (left lateral), 1.05 (right lateral), 0.82 (left anterior), 0.79 (right anterior), 0.87 (left posterior), and 0.79 (right posterior), without covert or overt corrective saccades (Figure 4).

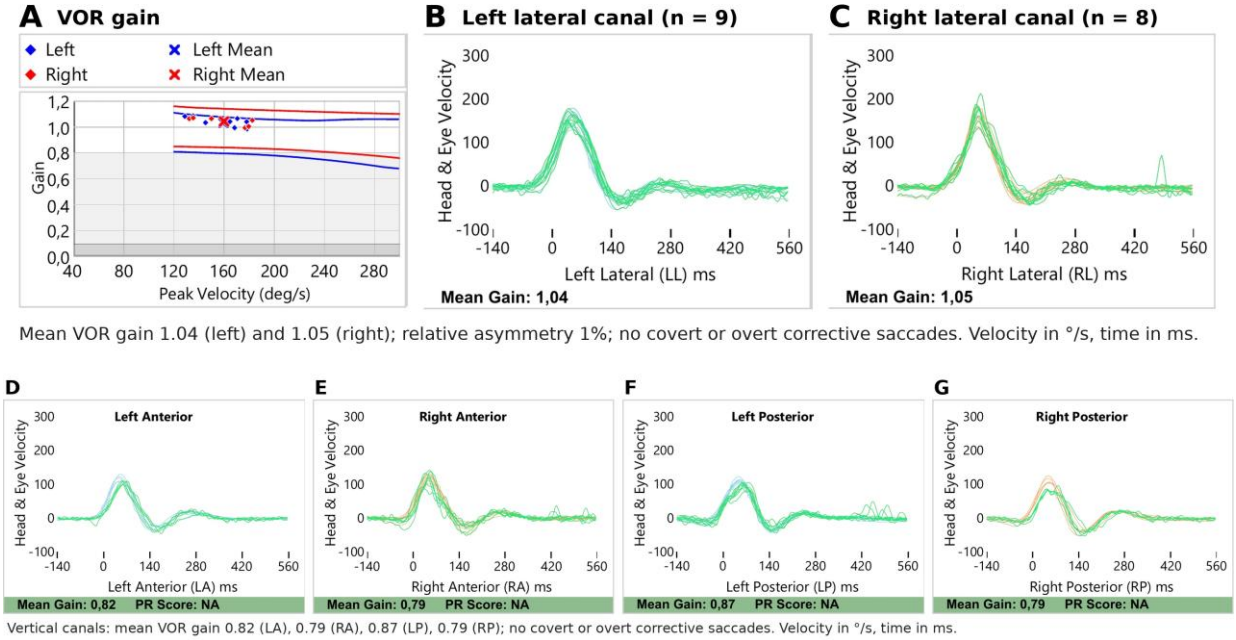


Figure 4. Video head impulse test. (A) VOR gain plotted against peak head velocity for left (blue) and right (red) lateral head impulses. (B, C) Head and eye velocity traces for left (n = 9) and right (n = 8) lateral impulses (mean gain 1.04 and 1.05; relative asymmetry 1%). (D–G) Head and eye velocity traces for the left anterior (D), right anterior (E), left posterior (F), and right posterior (G) canals (mean gain 0.82, 0.79, 0.87, and 0.79, respectively). No covert or overt corrective saccades were present in any canal. Velocity is shown in °/s and time in ms.

Otoscopy was normal, and tympanograms were type A bilaterally. Pure-tone audiometry showed bilateral sensorineural hearing loss with a sloping, predominantly high-frequency

configuration (Figure 5). Air-conduction thresholds at 0.25, 0.5, 1, 2, 3, 4, and 6 kHz were 15, 10, 35, 40, 60, 60, and 60 dB HL on the right and 25, 30, 50, 35, 60, 60, and 60 dB HL on the left, with a four-frequency pure-tone average (PTA; 0.5–4 kHz) of 36 and 44 dB HL, respectively, and a total hearing loss of 38.8% according to Fowler.

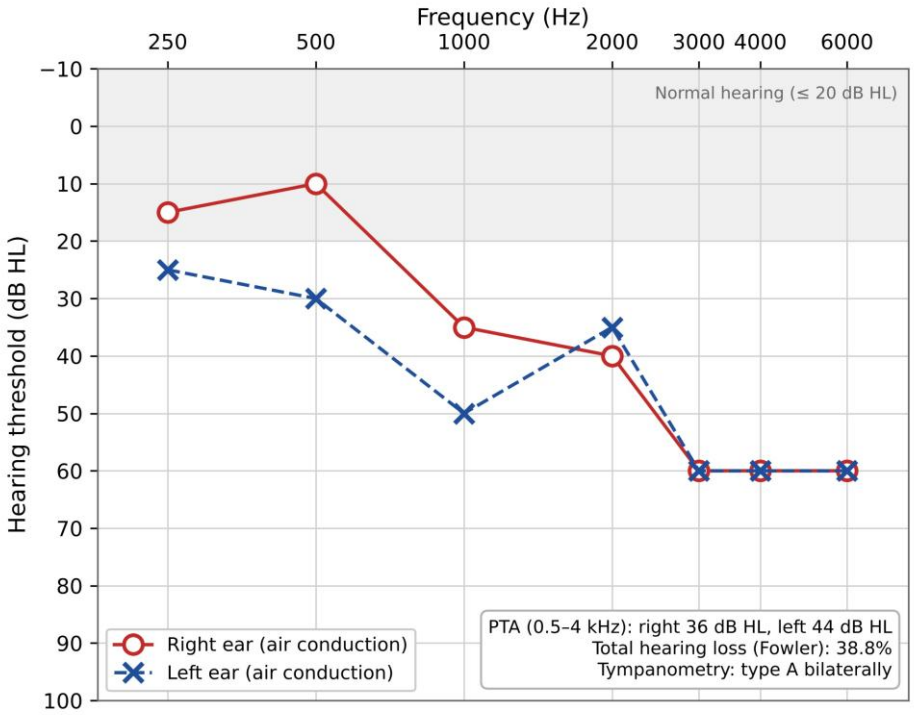


Figure 5. Pure-tone audiogram (air conduction), redrawn from the original record. Right ear, red circles (solid line); left ear, blue crosses (dashed line). The shaded area indicates normal hearing thresholds (≤20 dB HL).

The patient reported no photosensitivity. Examination revealed diffuse skin hyperpigmentation, most apparent on the lower limbs, and xeroderma (dry skin) of the lower legs (Figure 6).

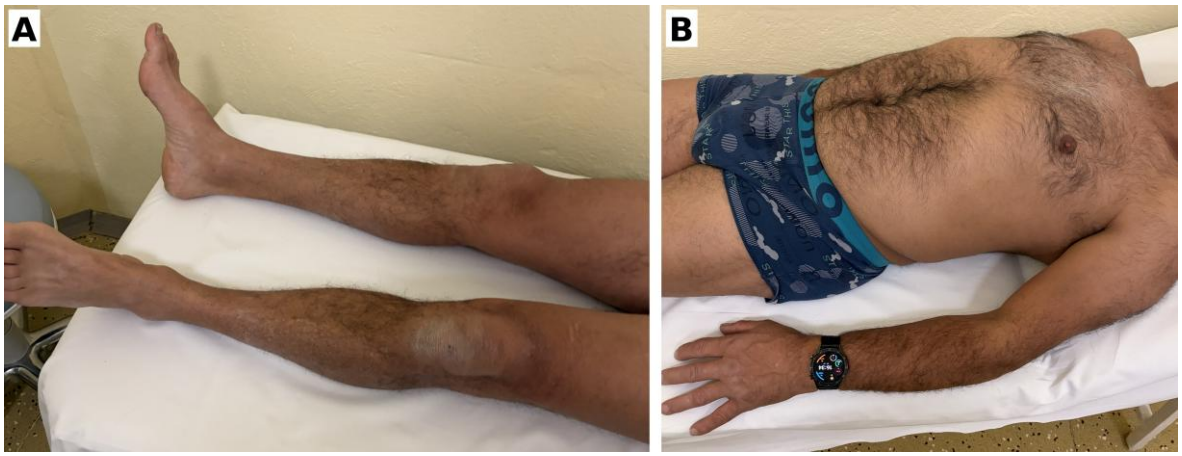


Figure 6. Clinical photographs. (A) Lower limbs with diffuse brownish hyperpigmentation and xeroderma (dry skin) of the lower legs. (B) Trunk and upper limb with diffuse hyperpigmentation.

Ophthalmological examination showed mild bilateral hyperopia, presbyopia, and bilateral retinal angiopathy, and optical coherence tomography was normal. The Mini-Mental State Examination (MMSE) score was 20/30, and neuropsychological evaluation demonstrated pathological deterioration of mnestic functions across all assessed domains, with confabulations and a practically absent capacity for new learning.

Laboratory and cerebrospinal fluid (CSF) investigations, including metabolic, vitamin, immunological, paraneoplastic, and infectious work-up, were mainly negative or non-specific (Supplementary Table 1). The patient received symptomatic treatment only and was discharged in a stable condition, with follow-up at our outpatient clinic.

3 Genetic Analysis

Repeat-expansion testing was negative for cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS, *RFC1*); spinocerebellar ataxia types 1, 3, 6, 7, 12, 17, and 27B (SCA27B, *FGF14*); dentatorubral–pallidoluysian atrophy; Huntington disease-like 2; fragile X-associated tremor/ataxia syndrome; and Friedreich ataxia (Supplementary Table 2).

Whole-exome sequencing (WES), with primary analysis of a virtual next-generation sequencing panel of genes associated with ataxia (HP:0001251) and cerebellar atrophy

(HP:0001272), identified the homozygous missense variant c.2395C>T, p.(Arg799Trp) in *ERCC4* (NM_005236.3; rs121913049), also reported as p.Arg788Trp. The variant is rare (gnomAD European allele frequency 0.075%), has predominantly pathogenic or likely pathogenic ClinVar submissions, is predicted to be damaging by 13 in silico tools (REVEL 0.51), and has been repeatedly reported in *ERCC4*-related neurodegeneration (3–6); it was classified as likely pathogenic according to ACMG/AMP criteria. The patient was diagnosed with *ERCC4*-associated xeroderma pigmentosum complementation group F with predominantly neurological manifestations (OMIM #278760), corresponding to NERDND (3). Two further homozygous variants of uncertain significance in *TMEM107* and *MT-ND5* were considered unrelated to the phenotype, and no clinically relevant copy number variants were detected. As a secondary finding, the patient was homozygous for *HFE* c.187C>G, p.(His63Asp), consistent with a mild form of hereditary haemochromatosis; serum ferritin and transferrin saturation were recommended but had not been performed at the time of assessment. Complete genetic results are given in Supplementary Table 2.

Homozygosity at three loci (*ERCC4*, *TMEM107*, and *HFE*), together with the common geographic origin of both parental families, suggested distant parental relatedness. Targeted segregation analysis of the *ERCC4* variant is planned in the patient's two siblings, and all of the patient's children are obligate asymptomatic heterozygous carriers. Genetic counselling was provided.

4 Systematic Review

4.1 Methods

The systematic review was conducted and reported according to the PRISMA 2020 statement (10). Using the PICO framework, the review question addressed which clinical, ocular motor, audiovestibular, imaging, and genetic features (outcomes) have been reported in adults with biallelic *ERCC4* variants or XP-F and neurodegeneration (population and exposure), compared

descriptively across patients and with the present case (comparison). PubMed/MEDLINE, Scopus, and Web of Science Core Collection were searched from inception to 5 November 2026, combining terms for the gene and disease, the neurodegenerative and ocular motor phenotype, and case reports or case series (Supplementary Table 3); the reference lists and literature reviews of included reports were also screened.

We included case reports and case series, including multicentre series with individual patient-level data, describing adults (≥18 years) with biallelic *ERCC4* variants or XP-F confirmed by complementation assay and progressive neurological deterioration involving the central nervous system. Reports of children, patients with variants in other NER genes or a purely cutaneous phenotype, reviews, conference abstracts, and articles not published in English were excluded. A generative AI tool (Claude, Anthropic) assisted with first-pass screening of records and with the identification of duplicate records and of reports describing the same patients; all decisions were verified independently by two reviewers (PS, MG), who also assessed the full texts, and disagreements were resolved by discussion. Data were extracted at the patient level, including the method of ocular motor assessment, and reports whose full text could not be obtained were included only if the patient's data were available from the abstract and from subsequent publications describing the same patient. Methodological quality was assessed using the tool of Murad et al., which evaluates selection, ascertainment, causality, and reporting (11). Data were synthesised descriptively. The detailed methodology is provided in the Supplementary Methods.

4.2 Results

The search identified 121 records; after removal of 26 duplicates, 95 records were screened and 19 reports were sought for full-text assessment. Ten reports describing 22 patients met the eligibility criteria (Figure 7), nine from the database search (3–7, 12–15) and one from the literature reviews of included reports (16). Reports excluded after full-text assessment are listed

in Supplementary Table 4. Detailed individual patient data are given in Table 1. Methodological quality was good in five reports and fair in three, whereas two reports, available only as abstracts and analysed together with subsequent publications describing the same patients, could not be fully appraised (Supplementary Table 5).

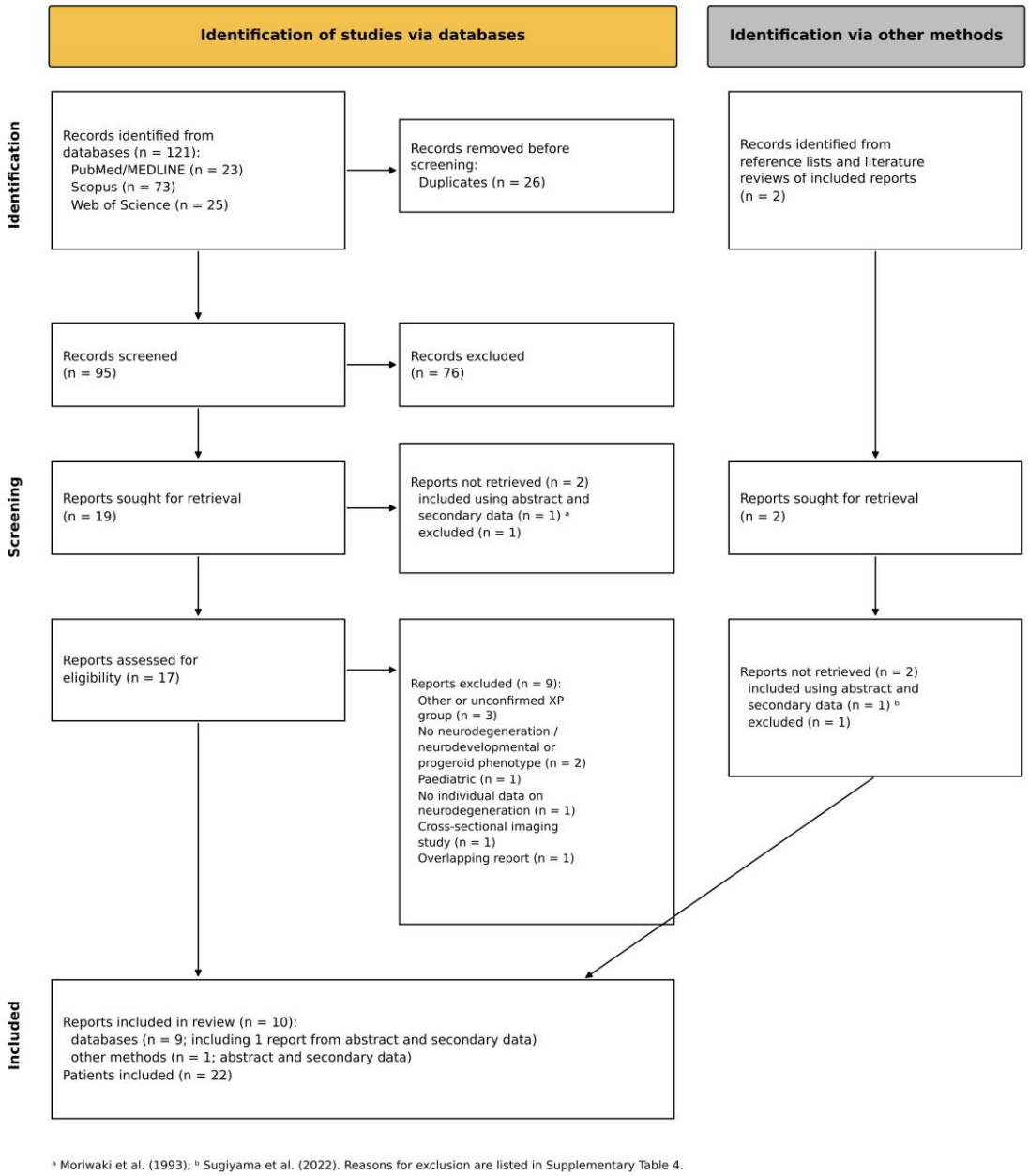


Figure 7. PRISMA 2020 flow diagram of the systematic review.

The 22 patients (10 men, 12 women) were described at a median age of 54 years (range 31–67), after a median disease duration of 10.5 years (range 1–38). Cerebellar ataxia, chorea, and

cognitive impairment were present in almost all patients, but their relative weight differed. An ataxia-predominant syndrome was most common (10 patients), followed by a mixed ataxia–chorea syndrome with prominent cognitive impairment and a dementia-predominant presentation (four patients each), a chorea-predominant, Huntington's disease-like syndrome (three patients), and a spastic–ataxic phenotype initially diagnosed as amyotrophic lateral sclerosis (one patient) (3). Brain MRI showed global or cerebellar–brainstem atrophy in all patients. The p.Arg799Trp variant was present in 19 patients, homozygous in four. Photosensitivity was common, whereas skin cancer was reported in only three patients (13, 15, 16).

Eye movements were mentioned in 18 patients, but specific findings were described in only nine, and quantitative recording had been performed in only one (5). The most frequent abnormalities were saccadic smooth pursuit and saccadic hypometria or dysmetria; slowed saccade initiation and antisaccade errors were each reported once (5, 6), and saccadic intrusions were not described in any patient. Hearing had been formally assessed in only 12 patients, and hearing loss was reported in 12, in some only subjectively; high-frequency hearing loss was found in two patients without subjective complaints (3). Vestibular function had been tested in only one patient, in whom the VOR was normal (5).

5 Discussion

This report combines a comprehensive clinical, genetic, ocular motor, vestibular, and audiological characterisation of a patient with genetically confirmed *ERCC4*-related neurodegeneration with a systematic review of 22 previously reported adult patients. The phenotype of our patient was multisystem, combining cognitive decline, pancerebellar ataxia, mild chorea, skin changes, distinct central ocular motor dysfunction, and audiovestibular involvement with sensorineural hearing loss and preserved peripheral vestibular function,

which illustrates the heterogeneity and diagnostic complexity of NER-related neurodegeneration (3).

The systematic review confirmed that *ERCC4*-related neurodegeneration is a slowly progressive disorder of adulthood, in which cerebellar ataxia, chorea, and cognitive impairment form the core of the phenotype. With a 13-year history and a pancerebellar syndrome, our patient corresponds to the most frequent, ataxia-predominant pattern, described particularly in the Japanese and French series (7, 14). However, the clinical presentation ranged from chorea-predominant, Huntington's disease-like syndromes (5, 6) to dementia-predominant and spastic–ataxic phenotypes (3, 15), so that the initial diagnosis frequently pointed to other neurodegenerative disorders. Chorea, present in almost all reported patients, was mild in our patient and may be easily overlooked. Severe mnestic impairment is consistent with the cognitive decline found in nearly all patients, and the combination of supratentorial atrophy with predominant cerebellar and brainstem atrophy corresponds to previous imaging reports (3, 7). Brisk tendon reflexes may indicate corticospinal involvement, as pyramidal signs were frequent in the reviewed patients, although a contribution of cervical spinal canal stenosis cannot be excluded.

Unlike most previously reported patients, our patient had no photosensitivity; skin involvement was limited to diffuse hyperpigmentation and xeroderma of the lower legs, supporting the concept that NERDND may present with minimal cutaneous signs (3, 5). The hyperpigmentation should be interpreted with caution, because the patient is also homozygous for *HFE* p.His63Asp, and iron studies have not yet been performed. Homozygous p.Arg799Trp has previously been associated with skin cancers from early adulthood (13), cerebellar ataxia with chorea (7, 14), and a chorea-predominant phenotype without ataxia (5), and in our patient with a multisystem phenotype without photosensitivity, illustrating marked phenotypic variability even with an identical genotype. At the extremes of the spectrum, *ERCC4* variants

cause childhood Fanconi anaemia with severe neurological complications (17) or purely cutaneous xeroderma pigmentosum when residual XPF function is preserved (18).

The review also showed that ocular motor function in *ERCC4*-related neurodegeneration has been described mostly qualitatively. Specific findings were available in fewer than half of the patients, consisted mainly of saccadic pursuit and saccadic hypometria or dysmetria, and had been recorded quantitatively in only one patient (5). In our patient, video-oculography showed excessive, heterogeneous saccadic intrusions, intermittent saccadic dysmetria with intermittent slowing of vertical saccades, slightly reduced vertical smooth pursuit gain, reduced optokinetic gains predominantly with vertical stimulation, and head-shaking–induced vertical nystagmus, whereas antisaccades were normal on clinical testing. Saccadic intrusions, which had not been reported in any previous patient, and saccadic dysmetria reflect impaired cerebellar control of saccades, particularly by the dorsal vermis and fastigial nuclei, whereas intermittent slowing of vertical saccades suggests additional involvement of the brainstem saccade generators, in line with the brainstem atrophy on MRI (19). The predominantly vertical impairment of smooth pursuit and optokinetic responses may reflect dysfunction of the flocculus and paraflocculus and their brainstem connections, and head-shaking–induced vertical nystagmus is a further central sign (19). Together, these findings indicate dysfunction of cerebellar and brainstem ocular motor networks and illustrate the value of video-oculography in objectifying it (8).

In contrast, vHIT showed normal VOR gain in all six semicircular canals without corrective saccades, indicating preserved peripheral vestibular function (9). Vestibular function had previously been tested in only one patient, in whom the VOR and verticality perception were normal (5). This is relevant for the differential diagnosis of late-onset cerebellar ataxia, as bilateral vestibulopathy is a defining feature of CANVAS (20) and is frequent in SCA27B (21); both conditions were also excluded genetically in our patient. Sensorineural hearing loss, however, was present, as in about half of the reviewed patients; hearing had been formally

assessed in only about half of them, and high-frequency loss was found even without subjective complaints (3). In xeroderma pigmentosum, hearing loss parallels neurological decline and is associated with degeneration of the cochlear sensory epithelium and neurons (22). The dissociation between impaired hearing and preserved peripheral vestibular function suggests selective involvement of the auditory system and supports systematic audiological assessment in these patients.

The diagnosis was established by WES only after approximately 13 years of symptoms, similar to the long disease duration before diagnosis in many reviewed patients. NERDND is probably underdiagnosed: NER disorders accounted for approximately 1% of previously unexplained ataxia and 8.6% of unexplained combined ataxia and dementia, and they should be considered even without dermatological manifestations or a positive family history (3). *ERCC4*-related neurodegeneration should therefore be considered in adults with a combination of cognitive decline, ataxia, and chorea, even when chorea is mild, skin changes are subtle, and the family history is not clearly positive. The ocular motor and audiovestibular profile, with central ocular motor dysfunction, preserved peripheral vestibular function, and sensorineural hearing loss, may support the clinical suspicion and guide genetic testing.

6 Conclusion

ERCC4-related neurodegeneration is a heterogeneous multisystem disorder that should be considered in adults presenting with a combination of cognitive decline, ataxia, chorea, skin changes, and hearing loss. Comprehensive ocular motor and audiovestibular assessment revealed central ocular motor dysfunction with preserved peripheral vestibular function and sensorineural hearing loss, findings that had been reported only qualitatively or not at all in previously described patients. Such profiling provides novel information on this rare disorder and should be included in the diagnostic work-up of these patients.

7 Limitations

This is a single case report, and its findings cannot be generalised; larger series are needed to establish how frequently this ocular motor and audiovestibular profile occurs. Evoked potentials were not performed, so a contribution of cervical myelopathy to the brisk reflexes cannot be excluded. Functional confirmation of impaired NER, segregation analysis, and iron studies were not available. Antisaccades were assessed clinically rather than by video-oculography. Age-related or occupational factors may have contributed to the high-frequency hearing loss, and the audiogram was reconstructed from a hand-drawn record with air-conduction thresholds only. No longitudinal ocular motor data were available. The systematic review was limited to English-language reports and three databases; two reports were analysed from abstracts and secondary sources, several findings in the largest series were reported only at cohort level, and the heterogeneous, mostly qualitative reporting of ocular motor and audiological findings did not permit pooled analysis.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Jessenius Faculty of Medicine (Approval No. EK 32/2023). Written informed consent to participate was obtained from the patient. Written informed consent for publication of the details and any accompanying images/videos was also obtained from the patient.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

PS drafted and wrote the manuscript and performed the systematic review. AB performed the clinical genetic evaluation and interpretation of the genetic findings. LCP performed the molecular genetic testing. MG contributed to study selection for the systematic review. SS, MG, and EK reviewed the manuscript and contributed to the analysis and interpretation of the data. All authors revised the manuscript critically for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Use of Generative Artificial Intelligence

The author(s) declare that generative AI was used in the preparation of this manuscript. Claude (Anthropic) was used for language editing, formatting, and editing of the figures, which are based on the authors' original clinical data, recordings and images. In the systematic review, it was also used to assist with first-pass screening of records and with the identification of duplicate records and overlapping reports; all decisions were verified independently by two reviewers. All content was reviewed and verified by the authors, who take full responsibility for it.

Data Availability Statement

The datasets analysed for this study are available from the corresponding author upon reasonable request. Data extracted for the systematic review are provided in Table 1 and the Supplementary Material.

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Table 1. Clinical, ocular motor, audiovestibular, imaging, and genetic data of adult patients with *ERCC4*-related neurodegeneration included in the systematic review and of the present case.

Study (case)	Sex; age; duration	Neurological features → dominant syndrome	Ocular motor findings (method)	Audiovestibular findings	Skin and systemic features	MRI and other investigations	*ERCC4* genotype; NER testing
Moriwaki et al. (12) [b]	M; 48 y [a]; 4 y	Cerebellar ataxia, chorea (upper limbs), cognitive impairment; no pyramidal signs or neuropathy → **Mixed ataxia–chorea with cognitive impairment**	NR (0)	NR	Freckles, mild photosensitivity; no skin cancer. Bile duct cancer (cause of death)	Cerebral atrophy; cortical and subcortical atrophy	c.1608_1617del10 / p.Arg454Trp ; XP-F by complementation; reduced repair in fibroblasts
Sijbers et al. (13)	M; 62 y; 15 y	Ataxic gait, limb dysmetria, dysarthria, mild chorea, restlessness; attention, recall, visuospatial and constructional deficits; mild axonal PNP; normal reflexes → **Ataxia-predominant**	Saccadic dysmetria (bedside, 1)	Audiogram normal; vestibular NR	Pigmented macules and telangiectasia from age 10, acute sunburn, very low MED; 9 BCC/SCC from 30s; mild photophobia, conjunctival injection	Marked cerebellar and cerebral cortical atrophy; EEG normal; SSEP/MEP: central conduction impairment; EMG: mild axonal PNP	Hom p.Arg799Trp (reported as R788W); UDS 22% of normal
Carré et al. (14), case 1	F; 31 y; 1 y	Cerebellar ataxia (SARA 8.5), mild diffuse chorea, brisk LL reflexes, right extensor plantar, pes cavus; mild subcortical–frontal cognitive profile; no PNP → **Ataxia-predominant**	Hypometric saccades (bedside, 1)	NR	Freckles; sunburn sensitivity (retrospective); no skin cancer	Cerebellar atrophy (isolated); EMG normal; fundoscopy normal	c.580_584+1delCCAAGG / p.Arg799Trp; segregation confirmed; NER ND
Carré et al. (14), case 2	M; 67 y; 27 y	Gait and limb ataxia (SARA 15), dysarthria, generalised chorea, bilateral Babinski, mild spasticity, absent ankle reflexes; dysexecutive and memory deficits (MMSE 25) → **Ataxia-predominant**	Saccadic pursuit (bedside, 1)	NR	Sunburn, persistent erythema, freckles, hypo-/hyperpigmentation; no skin cancer. Consanguinity	Cortical and severe cerebellar atrophy, diffuse WM changes; EMG: severe sensory axonal PNP	Hom p.Arg799Trp; CPD repair and UDS normal
Doi et al. (7), patient 1	F; 38 y; 8 y	Truncal and limb ataxia (SARA 9), dysarthria, mild choreiform movements, hyperreflexia, hypotonia; MMSE 29 (±) → **Ataxia-predominant**	Saccadic pursuit (bedside, 1)	Audiometry normal (15/5/5/15 dB)	Sunburn in childhood; normal to very mild lentigines; MED normal. Secondary amenorrhoea	Cerebellar, cerebral and brainstem atrophy, progressive (31→37 y); EEG 6-Hz phantom; NCS normal	c.577del (p.Trp193Glyfs*6) / p.Arg799Trp; reduced UDS
Doi et al. (7), patient 2	F; 35 y; 10 y	Truncal and limb ataxia (SARA 6.5), dysarthria, choreiform movements, hyperreflexia; MMSE 30 → **Ataxia-predominant**	Saccadic pursuit (bedside, 1)	NR	Sunburn in childhood; mild freckles; MED reduced. Secondary amenorrhoea	Cerebellar, cerebral and brainstem atrophy; EEG normal; NCS normal	c.577del (p.Trp193Glyfs*6) / p.Arg799Trp
Doi et al. (7), patient 3	F; 66 y; 23 y	Truncal and limb ataxia (SARA 11.5), dysarthria, choreiform movements, hyperreflexia; mild vibration and position sense loss; MMSE 26 → **Ataxia-predominant**	Saccadic pursuit (bedside, 1)	Hearing loss (35/32.5/40/47.5 dB at 0.5/1/2/4 kHz)	Sunburn in childhood; very mild lentigines; MED reduced. Consanguinity	Cerebellar, cerebral and brainstem atrophy; NCS normal	Hom p.Glu239Gln
Doi et al. (7), patient 4	M; 66 y; 38 y	Severe truncal and limb ataxia (SARA 29), dysarthria, choreiform movements, Gegenhalten, hyperreflexia; dementia (MMSE 17); epilepsy	Saccadic pursuit (bedside, 1)	Hearing loss (50 dB at 1 kHz, 40 dB at 4 kHz)	No sunburn history; mild freckles; MED markedly reduced. Consanguinity	Cerebellar, cerebral and brainstem atrophy; EEG: spikes on photic stimulation; NCS normal	Hom p.Arg799Trp

		→ Ataxia-predominant with dementia					
Shanbhag et al. (15), case 1	F; 60 y; 35 y	Presented with memory and balance problems; mild chorea (face, limbs), limb ataxia, mild ataxic dysarthria, dysphagia, absent ankle reflexes, extensor plantar; progressive cognitive decline (MoCA 16); walker **→ Dementia-predominant**	NR (0)	No subjective hearing loss; audiometry NA	Lifelong acute sunburn; moderate freckling; no skin cancer. Infertility	Severe global supra- and infratentorial atrophy; EMG/NCS: diffuse axonal sensorimotor PNP; sural biopsy: fibre loss	p.Arg589Trp / p.Arg799Trp; segregation confirmed; UDS 26% of normal
Shanbhag et al. (15), case 2	F; 54 y [a]; 36 y	Dystonia (head, neck), choreiform movements, appendicular tremor, ataxia, spasticity, brisk reflexes, extensor plantar; dementia; wheelchair, fully dependent **→ Dementia-predominant**	NR (0); optic disc pallor	Sensorineural hearing loss (onset mid-30s)	Blistering photosensitivity; ≥20 BCC from age 16	Severe global atrophy, inner-table hyperostosis; no PNP on EMG	p.Ser459* / p.Arg799Trp; segregation confirmed; UDS 21% of normal
Cordts et al. (3), ID 01	F; 60 y; 6 y	Ataxia (SARA 15), dysarthria, chorea (UHDRS-TMS 37), cognitive impairment (MoCA 11), spasticity, hyperreflexia, PNP; first diagnosed as HD-like **→ Mixed ataxia–chorea with cognitive impairment**	Saccadic abnormalities [c] (bedside, 1)	High-frequency SNHL without subjective complaint (audiometry 24/55 dB)	Skin type I–II; lentiginous pigmentation, signs of premature skin aging, reduced MED (50 mJ/cm²); no skin cancer. Sicca syndrome; infertility (IVF); urinary urgency	Global cerebral, cerebellar and brainstem atrophy; NfL 60 pg/ml	c.1069dup (p.Ile357AsnfsTer3) / p.Arg799Trp; segregation confirmed
Cordts et al. (3), ID 02	M; 48 y; 5 y	Ataxia, chorea, cognitive impairment (MoCA 20), PNP; no pyramidal signs; wheelchair; first diagnosed as hereditary ataxia **→ Ataxia-predominant**	Saccadic abnormalities [c] (bedside, 1)	Subjective hearing loss (hearing aids); audiometry NR	Dermatological examination not performed; no history of skin cancer. Urinary urgency	Global atrophy	c.580_584+1delCCAAGG / p.Arg799Trp
Cordts et al. (3), ID 03	M; 42 y; 5 y	Limb ataxia (SARA 10), chorea (UHDRS-TMS 25), mild athetosis, cognitive impairment (MoCA 13), PNP; no pyramidal signs; ambulatory **→ Ataxia-predominant with cognitive decline**	Saccadic abnormalities [c] (bedside, 1)	SNHL with hearing aids (audiometry 56/70 dB)	Skin type II; mild facial and upper-body freckling; no skin cancer. Keratopathy; urinary urgency	Global atrophy	c.580_584+1delCCAAGG / p.Arg799Trp; segregation confirmed
Cordts et al. (3), ID 04	F; 54 y; 10 y	Chorea (UHDRS-TMS 49), ataxia (SARA 21), dystonia, spasticity, hyperreflexia, PNP; wheeled walker; first diagnosed as HD-like **→ Chorea-predominant (HD-like)**	Saccadic abnormalities [c] (bedside, 1)	No subjective hearing loss; audiometry NR	Skin type II; lentiginous pigmentation, facial telangiectasia; no skin cancer	Global atrophy	c.516_517del (p.Thr173TrpfsTer37) / p.Arg799Trp
Cordts et al. (3), ID 05	F; 57 y; 19 y	Ataxia (SARA 25), chorea (UHDRS-TMS 38), cognitive impairment, mild spasticity, hyperreflexia, PNP; wheeled walker; first diagnosed as ataxia **→ Ataxia-predominant**	Saccadic abnormalities [c] (bedside, 1)	SNHL with hearing aids (audiometry 56/65 dB)	Skin type II; lentiginous pigmentation, rosacea (chin); no skin cancer. Sicca syndrome; primary ovarian insufficiency; urinary urgency	Global atrophy	c.904G>T (p.Asp302Tyr) / p.Arg799Trp

Cordts et al. (3), ID 06	F; 45 y; 20 y	Cognitive impairment as presenting and main feature (MoCA 22), ataxia (SARA 11), PNP; no chorea or pyramidal signs; first diagnosed as dementia **→ Dementia-predominant**	Saccadic abnormalities [c] (bedside, 1)	No subjective hearing loss; audiometry NR	Skin type II; lentiginous pigmentation; no skin cancer. Premature menopause; hepatocellular carcinoma 20 y after onset	Global atrophy; NfL 123 pg/ml	c.1081dupA (p.Met361Asnfs*4) / p.Arg799Trp; segregation confirmed
Cordts et al. (3), ID 07	M; 67 y; 7 y	Cognitive impairment (MoCA 15), chorea, ataxia (SARA 11), spasticity, hyperreflexia, PNP; first diagnosed as dementia **→ Dementia-predominant**	Saccadic abnormalities [c] (bedside, 1)	SNHL with hearing aids (audiometry 66/75 dB)	Skin type II; lentiginous pigmentation, reduced MED (65 mJ/cm²); no skin cancer	Global atrophy	c.2248C>T (p.Arg750Cys) / p.Arg799Trp
Cordts et al. (3), ID 08	M; 53 y; 8 y	Spastic paraparesis (severe spasticity, hyperreflexia), gait ataxia (SARA 11), mild chorea, mild cognitive impairment (MoCA 25, UHDRS-TMS 18); no PNP; first diagnosed as ALS **→ Spastic–ataxic (motor neuron disease-like)**	Saccadic abnormalities [c] (bedside, 1)	High-frequency SNHL without subjective complaint (audiometry 18/53 dB)	Skin type III; lentiginous pigmentation with hypopigmented areas, signs of premature skin aging, facial telangiectasia, suspected actinic keratosis; no skin cancer	Global atrophy	Hom p.Arg750Cys
Sugiyama et al. (16) [b]	M; 60 y; 16 y	Gait ataxia, dysarthria, chorea, polyneuropathy, upper motor neuron signs; mild cognitive impairment **→ Mixed ataxia–chorea with cognitive impairment**	Oculomotor abnormalities reported, not specified	No hearing loss reported	Photosensitivity, freckles; 1 BCC	Prominent cerebellar atrophy, diffuse brainstem and cerebral atrophy	p.Arg799Trp + p.Ser805Pro + p.Gly912Arg (cis); DNA repair test abnormal
Kulikowska et al. (4)	F; 53 y; 11 y	Falls and balance disorder, then chorea (upper limbs, head), tongue stereotypies, cerebellar ataxia, dysarthria; executive dysfunction **→ Mixed ataxia–chorea with cognitive impairment**	NR (0); ophthalmology normal	Bilateral sensory hearing loss (otolaryngology)	Sun and conjunctival hypersensitivity from childhood; pigmented lesions; no skin cancer. Premature ovarian failure; hereditary spherocytosis (SPTB variant, splenectomy); B12-deficiency anaemia	Massive cortico-subcortical (supratentorial) atrophy; ENG normal	p.Trp450Ter / p.Arg799Trp; segregation confirmed
Barthel et al. (5)	F; 62 y; 12 y	Chorea of distal limbs, face and jaw, vocalisations; no ataxia; working memory, executive deficits, psychomotor slowing without dementia **→ Chorea-predominant (HD-like)**	Saccadic pursuit; hypometric saccades with normal latency and peak velocity; antisaccade errors >50%; no gaze-evoked nystagmus (quantitative, 2)	Mild age-related hearing loss (audiogram); VOR and verticality perception normal	Lifelong sun sensitivity, heavy sunburns; no skin cancer	Fronto-parietal and cerebellar atrophy, sparing of mesial temporal lobe and caudate; putaminal iron, pallidal Ca^{2+} (QSM); normal WM; NfL 44 pg/ml; ENG normal	Hom p.Arg799Trp (gene panel)
De Cleene et al. (6)	M; 33 y; 1 y	Generalised chorea, mild gait ataxia, dysdiadochokinesia, brisk reflexes; executive dysfunction, verbal memory deficit **→ Chorea-predominant (HD-like)**	Slowed saccade initiation; no nystagmus (bedside, 1)	Mild bilateral hearing loss (subjective, not tested)	Photosensitivity, freckle-like facial pigmentation; seborrhoeic keratosis	Global atrophy, mainly cerebellum and brainstem; FDG-PET: cerebellar, bithalamic, bitemporal hypometabolism; NCS normal	c.1811+1G>A / p.Arg799Trp; segregation confirmed
Present case	M; 58 y; 13 y	Pancerebellar syndrome (SARA 14–15), mild dysarthria, mild generalised chorea, brisk reflexes; amnestic cognitive decline (MMSE 20)	Excessive saccadic intrusions (SWJ, MSWJ, pulses, staircase oscillations); intermittent saccadic dysmetria, vertical slowing; reduced vertical	Bilateral sloping high-frequency SNHL (PTA 36/44 dB); vHIT normal in all six canals	No photosensitivity; diffuse hyperpigmentation, xeroderma of legs	Severe cerebellar, mild brainstem and global cerebral atrophy (progressive since 2012)	Hom p.Arg799Trp (WES)

		→ Ataxia-predominant with cognitive decline	pursuit and OKN gain; head-shaking vertical oscillations (VNG, 2)				

Duration, time from the onset of neurological symptoms to the last report. Ocular motor method: 0, not reported; 1, bedside examination; 2, quantitative recording.

[a] Age at death. [b] Full text not available; data from the abstract and from subsequent reports describing the same patient, i.e. Carré et al. (14) for Moriwaki et al. and Barthel et al. (5) and De Cleene et al. (6) for Sugiyama et al. [c] Saccadic abnormalities were reported in all patients of the series but not specified per patient; a history of sunburn was reported only at cohort level; audiometry values are given as four-frequency pure-tone average / high-frequency average.

ALS, amyotrophic lateral sclerosis; BCC, basal cell carcinoma; CPD, cyclobutane pyrimidine dimer; EEG, electroencephalography; EMG, electromyography; ENG, electroneurography; F, female; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; HD, Huntington's disease; Hom, homozygous; IVF, in vitro fertilisation; LL, lower limb; M, male; MED, minimal erythema dose; MEP, motor evoked potentials; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MSWJ, macro square-wave jerks; NA, not available; NCS, nerve conduction studies; ND, not done; NER, nucleotide excision repair; NfL, neurofilament light chain; NR, not reported; OKN, optokinetic nystagmus; PNP, polyneuropathy; PTA, pure-tone average; QSM, quantitative susceptibility mapping; SARA, Scale for the Assessment and Rating of Ataxia; SCC, squamous cell carcinoma; SNHL, sensorineural hearing loss; SPTB, spectrin beta gene; SSEP, somatosensory evoked potentials; SWJ, square-wave jerks; UDS, unscheduled DNA synthesis; UHDRS-TMS, Unified Huntington's Disease Rating Scale – Total Motor Score; vHIT, video head impulse test; VNG, videonystagmography; VOR, vestibulo-ocular reflex; WES, whole-exome sequencing; WM, white matter; XP-F, xeroderma pigmentosum complementation group F.

Supplementary Videos

Supplementary Video 1. Examination of cerebellar function in the upper limbs, showing bilateral dysmetria, dystaxia, and dysdiadochokinesia, together with mild generalised chorea.

Supplementary Video 2. Examination of cerebellar function in the lower limbs, showing bilateral dysmetria and dystaxia.

Supplementary Video 3. Ataxic gait with marked difficulty in tandem gait.

Supplementary Video 4. Video-oculographic recording of saccadic oscillations.

Supplementary Files

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