Cerebellar ataxia, neuropathy, vestibular areflexia syndrome: genetic and clinical insights

Roisin Sullivan\textsuperscript{a,\ast}, Rauan Kaiyzhanov\textsuperscript{a,\ast,\ast}, and Henry Houlden\textsuperscript{a,\ast}

Purpose of review
This review aims to summarise the present cerebellar ataxia, neuropathy, vestibular ataxia syndrome (CANVAS) literature, providing both clinical and genetic insights that might facilitate the timely clinical and genetic diagnosis of this disease.

Recent findings
Recent advancements in the range of the clinical features of CANVAS have aided the development of a broader, more well-defined clinical diagnostic criteria. Additionally, the identification of a biallelic repeat expansion in RFC1 as the cause of CANVAS and a common cause of late-onset ataxia has opened the door to the potential discovery of a pathogenic mechanism, which in turn, may lead to therapeutic advancements and improved patient care.

Summary
The developments in the clinical and genetic understanding of CANVAS will aid the correct and timely diagnosis of CANVAS, which continues to prove challenging within the clinic. The insights detailed within this review will raise the awareness of the phenotypic spectrum and currently known genetics. We also speculate on the future directions of research into CANVAS.

Keywords
bilateral vestibular failure, cerebellar ataxia with neuropathy and vestibular areflexia syndrome, cerebellar ataxia, neuropathy, repeat expansion, RFC1

INTRODUCTION
Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a late-onset slowly progressive neurodegenerative ataxic disorder. There have been numerous publications defining the clinical spectrum and the pathological and genetic basis of this disease. These multidisciplinary and successional studies have expanded our understanding of CANVAS as a multisystem disease with a pattern of spatial progression and variable phenotype. Despite the accumulated knowledge, it seems that the suspicion and diagnosis of CANVAS still remain challenging in nonspecialist clinic settings and regions with no access to genetic testing. This review aims to integrate the important findings of the present CANVAS literature and provide clinico-genetic insights that might aid the timely diagnosis of CANVAS.

CHRONOLOGICAL OVERVIEW OF CEREBELLAR ATAXIA WITH NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME LITERATURE
From a chronologic perspective, CANVAS literature can be divided into 3 periods. The initial period includes papers published by neuro-otologists between 1991 and 1998, primarily addressing the role of the cerebellum in the compensatory ocular reflexes after bilateral vestibular failure (BVF) [1–3]. The following period from 2004 until 2018, when CANVAS had evolved into a distinct clinical entity with described neuropathology, proposed clinical criteria, and suspected but unknown genetic cause [4–10]. The recent period starting from 2019 discovers the common genetic cause of CANVAS and further expands our understanding of this disease.

\*Department of Neuromuscular Disease, University College London and \#The National Hospital for Neurology and Neurosurgery, London, UK

Correspondence to Roisin Sullivan, Department of Neuromuscular Disease, University College London, London, UK.

E-mail: r.sullivan@ucl.ac.uk

\textsuperscript{\ast}\textsuperscript{\ast}These authors contributed equally.

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The early publications (1991–2004) provided a unique contribution by going further than the highlighted association between BVF and cerebellar ataxia (CA). Despite the limited number of cases, the early reports picked up and described the currently known important features of CANVAS as peripheral neuropathy and downbeat nystagmus, albeit no association with the CA-BVF was made. Nevertheless, this has probably played a role in the definition of full CANVAS as subsequent studies deliberately sought the presence of peripheral neuropathy in larger cohorts. We anticipate that the fourth period of publications will address other genetic and mechanistic causes of CANVAS. Figure 1 depicts the available CANVAS literature in chronological order and provides a brief summary of the findings.

**CLINICAL PRESENTATION**

Clinically defined and recently genetically confirmed series of CANVAS has helped to delineate its phenotype over time. Currently, we know that CANVAS clinically expresses predominantly late-onset, slowly progressive, severe imbalance with absent visually enhanced vestibulo-ocular reflex (VVOR) (a hallmark sign) suggesting combined bilateral vestibular and cerebellar dysfunction in the setting of nonlength dependent sensory deficits (a diagnostic triad). CANVAS has a number of additional symptoms, the most frequent ones being an autonomic failure and chronic spasmodic cough, which could start 15–29 years before gait imbalance and can even form ‘the ataxia chronic cough’ phenotype cluster [16*,17] (Table 1). A caveat is that a subgroup of CANVAS cases could remain with an incomplete triad for many years due to phenotypic variability [8,12*]. Evidence from a 100 genetically confirmed CANVAS cohort has suggested that the complete triad might be present in only 2/3 of cases and that neuronopathy is a ubiquitous sign of CANVAS [12*].

According to the genetic series, the mean onset for any neurological sign of CANVAS (cough excluded) is 52 years, albeit the onset might range between 19 and 76 years [12*]. Thus, young adults could also develop CANVAS symptoms. Half of CANVAS cases might manifest with a progressive motion-dependent postural imbalance, typically exacerbating in darkness and causing dizziness and/or falls. Although, the onset with isolated sensory symptoms or oscillopsia is possible [12*].

Each component of the CANVAS triad can cause postural imbalance independently but when combined, they result in impaired VVOR and severe imbalance leading to significant disability. All CANVAS symptoms have an insidious onset, particularly BVF due to simultaneous compensation mechanisms. Oculomotor testing is very important for CANVAS diagnosis as it can reveal the signs of BVF and/or cerebellar dysfunction. VVOR reflects a combined failure of all three compensatory eye movement systems, namely, vestibulo-ocular reflex (VOR), smooth pursuit, and optokinetic reflex [18]. It can be demonstrated at the bedside by turning a patient’s head slowly from side to side. The test is considered positive if compensatory eye movements are saccadic rather than smooth. Video-oculography, videonystagmography, or rotational chair testing can determine the degree of VVOR impairment [9]. Studies of vestibular evoked myogenic potentials measuring saccular and utricular function showed inconsistent results in CANVAS [19,20].

CA in CANVAS typically manifests with cerebellar-type ocular motor impairment including downbeat nystagmus, broken pursuit, gaze-evoked nystagmus, and saccadic dysmetria [4,7,8,18,21,22]. Appendicular incoordination, truncal ataxia, and cerebellar-type dysarthria can precipitate typically 2–6 years after the onset of gait impairment [12*]. A pattern of spatial progression from sensory neuronal involvement early on, to later vestibular and cerebellar dysfunction has been suggested [12*].

Neuropathy in CANVAS clinically presents with a multimodal nonlength-dependant sensory deficit, frequently associated with normo- or hyperreflexia. Electrophysiology studies reveal severe axonal sensory neuropathy with a reduced or absent sensory nerve action potentials (SNAP) in upper- and lower limbs (neuropathy), relatively intact motor conduction and F-wave latencies but reduced H-reflexes.
Electromyography is typically normal [6,9,12]. Normoreflexia is explained by the sparing of muscle spindle afferents (Ia fibers) [23,24]. Peripheral nerve ultrasound studies showed that nerves of CANVAS patients are significantly smaller than their age- and gender-matched controls, which is consistent with neuronopathy [25,26].

Brain MRI data has suggested a pattern of cerebellar atrophy, corresponding to the neuropathological findings. This includes predominant hemispheric atrophy in the posterosuperior and horizontal fissures, delimiting Crus 1, and associated with this anterior and dorsal vermial atrophy (lobules VI, VIIa, and VIIb) [8,18]. Mild brain stem atrophy and posterior cord atrophy are also seen on brain and spinal cord MRI respectively [12].

Despite the proposed clinical criteria, even full CANVAS seems to escape clinical suspicion and/or diagnosis, exemplified by only 23 out of 66 genetically confirmed patients with full CANVAS having received the initial diagnosis of CANVAS [12]. This might suggest that further work needs to be done to increase the awareness of CANVAS among medical professionals.

**NEUROPATHOLOGY OF CEREBELLAR ATAXIA WITH NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME**

Oto-and neuropathology studies of CANVAS have suggested that widespread ganglionopathy (neuronopathy) is a hallmark of CANVAS that underlies...
peripheral sensory deficit, vestibular areflexia, and dysautonomia [7,27]. This was shown by sub-total neuronal loss of the sensory nerve ganglia of the dorsal root of the spinal cord with resultant posterior column atrophy and associated axonal neuropathy. The anterior and lateral horns of spinal cord appeared normal. Additionally, a multiple cranial nerve neuronopathy affecting the vestibular, facial, and trigeminal nerves has been demonstrated [27]. Selective atrophy of the vestibular nerves and marked loss in Scarpa’s ganglion cells with intact auditory nerve and the spiral (cochlear) ganglion were also observed. The normal population of hair cells and supporting cells were demonstrated in the cristae and maculae [27]. The most significant cerebellar pathology was a neuronal loss in the Purkinje cells with the preferential atrophy of the anterior and dorsal vermis (lobules VI, VIIa, and VIIb) and hemispheric crus I. The cerebellar dentate nuclei, basal ganglia, and diencephalon appeared intact [7]. Currently available oto-and neuropathology studies derive from four cases with a clinically based and one case of a genetically confirmed diagnosis of full CANVAS.

### CEREBELLAR ATAXIA WITH NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME LOOK-ALIKES AND CLUES TO THE DIAGNOSIS OF CEREBELLAR ATAXIA WITH NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME

Progressive ataxia resulting from variably combined impairments in proprioceptive, vestibular, and cerebellar functions is not specific to CANVAS. The diagnostic workup should start by excluding curable disorders with underlying nutritional, immune-mediated, and paraneoplastic causes. Afterward, the main differential diagnosis should include multisystem atrophy cerebellar variant (MCA-C) and genetic disorders such as Friedreich ataxia, SCA3, SCA1, SCA6, and the nuclear POLG1 gene. More details on the suggested differential diagnosis are given in Table 2. With the discovery of the genetics cause of CANVAS it is plausible to test cases suggestive of CANVAS for RFC1 expansions first, if genetic testing is possible, then if negative to investigate for other genetic causes.

CANVAS can usually be diagnosed clinically. However, the diagnosis may be more challenging in those cases where a significant delay in the manifestation of all three cardinal features exists, e.g., CANVAS in evolution, and the onset age of the first signs is <60 years, particularly in sporadic patients. The final component of the diagnostic triad may take more than 10 years [8]. Ataxia is usually an overt sign of CANVAS, whereas neuropathy and BVF could be subclinical requiring their deliberate and regular search using specialised tests. There are certain clues to the diagnosis of CANVAS that should prompt a purposeful search for other components of the diagnostic triad (Fig. 2A). Invaluable help in the clinical diagnosis of CANVAS comes from a description of large genetically confirmed CANVAS cases and the proposed clinical diagnostic criteria. Considering a range of CANVAS-associated features that are not reflected in the current diagnostic criteria, might also be important in the clinical diagnosis.

### GENETICS OF CEREBELLAR ATAXIA WITH NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME: RFC1 EXPANSION

CANVAS has largely been thought of as a sporadic disease; however, affected sibships suggest a genetic

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**Table 1. CANVAS/RFC1 CANVAS associated features**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (references)</th>
</tr>
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<tbody>
<tr>
<td>Downbeat nystagmus</td>
<td>65% [21]</td>
</tr>
<tr>
<td>Spasmodic cough</td>
<td>64% [13]</td>
</tr>
<tr>
<td>Normoreflexia</td>
<td>50% [13,24]</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>42/100 [13]</td>
</tr>
<tr>
<td>Oscilllopia</td>
<td>32% [13]</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>27% [13]</td>
</tr>
<tr>
<td>Autonomic features</td>
<td>32% (50% of those undergoing specific investigations), 91%, 44%, [5,21,16*]</td>
</tr>
<tr>
<td>Cold and pale feet</td>
<td>78% [21]</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>65% [21]</td>
</tr>
<tr>
<td>Xerostomia/xerophthalmia</td>
<td>52% [21]</td>
</tr>
<tr>
<td>Postural instability with retropulsion</td>
<td>49% [16*]</td>
</tr>
<tr>
<td>REM sleep behaviour disorder</td>
<td>40–70% [14]</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>31% [16*]</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>7%, 78%, 44% [13,16*,21]</td>
</tr>
<tr>
<td>Persistent constipation</td>
<td>7%, 65%, 24% [13,16*,21]</td>
</tr>
<tr>
<td>Reduced feet sweating</td>
<td>48% [21]</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>25% [16*]</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>13–30% [13,21,16*]</td>
</tr>
<tr>
<td>Urinary leakage</td>
<td>8%, 39% [13,21]</td>
</tr>
<tr>
<td>Bradikinesia</td>
<td>28% [16*]</td>
</tr>
<tr>
<td>Nausea, vomiting, and bloating after small meal</td>
<td>26% [21]</td>
</tr>
<tr>
<td>Slowing of vertical saccades</td>
<td>17% [16*]</td>
</tr>
<tr>
<td>Hyperkinetic movement disorders</td>
<td>5% [16*]</td>
</tr>
<tr>
<td>Sudomotor dysfunction</td>
<td>[17]</td>
</tr>
<tr>
<td>Neurotrophic Keratopathy</td>
<td>[21]</td>
</tr>
</tbody>
</table>

CANVAS, cerebellar ataxia, neuropathy, vestibular areflexia syndrome; REM, rapid eye movement.
| Table 2. Recommended differential diagnosis in CANVAS |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | CANVAS | FRDA  | SCA3 | SCA1 | SCA6 | ANS-POLOG disorders |
| Gene                            | RFC1   | FXN   | ATXN3| ATXN1| CACNA1A| POLG           |
| Typical age of onset            | Late adulthood (mean 52yrs) | < 25 yrs | 30–40yrs | 30–40yrs | 43–52 years | 2nd-4th decade |
| Progression                     | Slow   | Slow  | Could be rapid depending on the number of CAG repeats | Slow | Slow | Typically rapid |
| Neuropathy                      |         |       | Typical age of onset |       |       | Subacute onset |
| Progression                     | Progressive | Progressive | Progressive | Progressive | Progressive | Progressive |
| Cerebellar ataxia               |         |       |       |       |       | Yes |
| Neurpathy                       |         |       |       |       |       | Part of the classic triad |
| BVF                             | Progressive, typically severe | Mild | Yes, Mild to moderate | Yes, Mild | No | Yes |
| Chronic cough                   | Frequent | No | No | No | No | No |
| Dysautonomia                    | Postganglionic AF, Frequent, Mild, Late presentation | Rare, Late presentation, mild | Frequent (67–70%), Mild to moderate | Frequent (22–100%), Mild to moderate | No | Very rare |
| DBN                             | Frequent | Rare | No | No | No | Yes |
| Brain MRI features              | Cerebellar atrophy involving anterior and dorsal vermis, as well as the hemispheric crus | Significant grey and white matter loss in the deep cerebellar nuclei and brainstem, significant atrophy in the superior cerebellar peduncles | Cerebellar, cerebral cortical, and pontine atrophy, ’Hot cross bun sign’ | Olivopontocerebellar atrophy (OPCA) and white matter (WM) atrophy, ’Hot cross bun sign’ | Pure cerebellar atrophy, ’Hot cross bun sign’ | Atrophy or abnormal signal intensity in the cerebellum brainstem, and other brain structures |
| Other distinguishing features   | Impaired VVOR | Normoreflexia | Frequent muscle weakness, pyramidal involvement (Babinski signs) & skeletal deformities (pes cavus, scoliosis) | Pyramidal and extrapyramidal signs, Amyotrophy fasciculations | Pyramidal signs, cognitive decline | Encaphalopahty with seizures |
|                                 |         |       | Assoc cardiomyopathy & diabetes | Vision & hearing loss | | Ophthalmoplegia |
|                                 |         |       | Multisystem involvement | | | Parkinsonism, RBD (frequent) |
|                                 |         |       | | | | Acute confusion, impaired vision and hearing, psychosis |
component \cite{11}. Recently a biallelic intronic expansion in \textit{RFC1} has been identified as a cause of sporadic late-onset ataxia and CANVAS, with a core ancestral haplotype that most likely arose 25,000 years ago in Europe \cite{11,13}.

The biallelic \textit{RFC1} expansion has been confirmed in a range of populations and ethnicities. The pentanucleotide AAGGG\((n)\) carrier frequency within the normal population ranges between 0.7 and 6.8% \cite{11,13,28–30}. Several studies have identified the recessive \textit{RFC1} expansion in 90% of patients with full CANVAS, 20–22% of patients with late-onset ataxia and/or peripheral neuropathy, around 60% with cerebellar involvement and sensory neuropathy and 3.2% with undiagnosed CA \cite{5,13,21}. Non-European, unselected late-onset ataxia cohorts of Turkish, West-Asian, and Indonesian ethnicity were found to have an \textit{RFC1} frequency rate of 14%, showing that \textit{RFC1}-related disease is extending globally, which could also be influenced by higher consanguinity rates \cite{16}.

Contrastingly, several studies have reported lower or absent rates of the \textit{RFC1} repeat expansion in certain populations including Canadian and Brazilian late-onset ataxia, Japanese familial and sporadic late-onset ataxia, and Chinese Han ataxia cohorts \cite{28,29,31}.

\textbf{REPEAT MOTIFS}

The \textit{RFC1} locus is highly polymorphic, spanning the pathogenic conformation AAGGG\((n)\), the reference AAAAG\((11)\), expanded AAAAG\((n)\) and AAGGG\((n)\). The allelic distribution of these has been identified as 75.5%, 13.0%, and 7.9%, respectively, within the control population \cite{11}. Three percent were undetermined and most likely correspond to novel conformations that include AAGAG\((n)\) and AGAGG\((n)\), that have, as yet, uncertainty concerning their possible pathogenicity \cite{28}. Two novel pathogenic conformations were identified in Asian Pacific cohorts. A likely pathogenic recessive ACAGG\((n)\) motif was identified in Asian Pacific and Japanese cohorts \cite{15,31}. An alternate pathogenic allele configuration (AAGGG\((10–25)\) AAGGG\((n)\) AAGGG\((n)\)) was found to be specific to the Māori population, that had no phenotypic differences to European cohorts \cite{14}.

The various motif conformations follow a pattern in expansion size; with pathogenic AAGGG\((n)\) ranging from 400 to 2000 repeating units, AAAGG\((n)\) from 40 to 1000 and AAAAG\((n)\) with 15 to 200 repeats \cite{11}. There is a positive correlation between \textit{RFC1} expansion size and GC content, with each listed motif containing 20%, 40%, and 60% GC content, respectively \cite{15}. There has been no correlation observed between the size of expansion and age of onset, symptom onset (cough excluded) and severity of disease \cite{12}. There are likely to be further novel repeat motifs that have evaded detection due to high GC content and consequential low coverage, exemplified by the historic challenge of
sequencing the GC-rich GGGGCC repeat expansion in C9orf72 and discovery of the VWA1 repeat expansion in recessive hereditary motor neuropathy; both of which have GC content implicated in pathogenicity [32,33]. GC content has been shown to increase mutation rates, with an altered yeast gene with 63% GC content showing a > 6-fold increased mutation rate [34].

**RFC1 PATHOLOGICAL MECHANISM**

The pathological mechanism underlying the biallelic repeat expansion in RFC1 is currently unknown. RFC1 is a large subunit of the RFC complex that loads and unloads proliferating cell nuclear antigen onto DNA [35,36]. The biallelic expansion in RFC1 is located at the 3’-end of a deep intronic AluSx3 element. Alu elements undergo insertions into new genomic locations and contribute to genetic instability, potentially contributing to age-related degeneration [37,38]. The polyA tail at the 3’ end of the Alu element is theorized to be a microsatellite expansion initiation site and undergoes A-tail shortening which has resulted in the majority being inactive [37,39]. The shared core haplotype and highly polymorphic polyA tail supports evidence of an original genetic event predicted to have occurred during the Alu element polyA-tail shortening and degradation process; with AAAAG changing to AAAGG or AAAGG in a more recent common ancestor 25,000 years ago [13].

The RFC1 expansion does not cause an associated loss of function of the RFC1 protein and RNA-seq did not implicate any bordering or distant genomic regions [11**]. RFC1 has been associated with DNA damage recognition, DNA repair enzyme interaction, DNA enzyme recruitment and pathways that include nucleotide excision repair [40]. Ataxia and neuropathy are features of many neurodegenerative diseases suggesting that the peripheral nerves and cerebellum are particularly vulnerable to DNA damage [41]. However, response to DNA repair was found to be normal within fibroblast lines with the biallelic RFC1 repeat expansion [11**].

Repeat expansions within transcripts are implicated in altered splicing machinery; RNA foci and RNA toxicity are features of myotonic dystrophy type 1 (DM1) and 2 (DM2) [42]. Repeat-associated non-ATG (RAN) proteins are also implicated in diseases such as C9orf72 Amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD), with their accumulation affecting downstream pathways [43]. However, CANVAS brain tissue with RFC1 biallelic expansion showed no sense or antisense RNA foci. Similarly to other diseases with GC rich intronic expansions such as C9orfALS/FTD and DM2, intronic retention has been observed across all tissues in CANVAS patients, affecting intron 2 in RFC1 premRNA [11**,44]. This finding could be key to elucidating the pathogenic mechanism underpinning the RFC1 repeat expansion as intronic retention, and therefore impaired pre-mRNA processing, can affect nuclear retention and nucleocytoplasmic transport of pre-mRNA.

**MOLECULAR DIAGNOSIS OF RFC1**

Molecular diagnosis of CANVAS consists of a combination of flanking polymerase-chain reaction (PCR), repeat-primed PCR (RPPCR) and Southern blotting to confirm the presence of the biallelic RFC1 expansion (Fig. 2B). Patients positive for the biallelic repeat expansion will show no amplifiable product on flanking PCR, a positive trace on RPPCR (which resembles a hallmark sawtooth decremental peak pattern), and distinct bands on Southern blotting corresponding to the expanded alleles. Long-read sequencing has also been shown to precisely identify the biallelic RFC1 repeat expansion and has the potential to replace Southern blotting as the gold-standard in genetic diagnosis [45]. Despite the intronic location of the RFC1 repeat expansion, the AAGGG motif has also been identified using whole-genome- and exome-sequencing (WGS/WES). If successfully validated it could prove a useful screening tool for existing WGS and WES datasets in the identification of currently undiagnosed RFC1 positive patients [34].

**PHENOTYPIC SPECTRUM OF RFC1 EXPANSION**

The phenotypic spectrum implicated with the RFC1 expansion is broadening. Whilst the biallelic RFC1 repeat expansion has been found to be absent in pathologically confirmed MSA, positive cases have been reported with clinically confirmed MSA [29,46,47]. The biallelic RFC1 expansion has been associated with unspecified, late-onset ataxia, dopa-responsive parkinsonism, hereditary sensory neuropathy with cough and Sjögren syndrome and [48–50]. Furthermore, a recent series of RFC1 CANVAS has suggested that RFC1-disease presents with multisystemic phenotypes overlapping with MSA-C, progressive supranuclear palsy, and hyperkinetic movement disorders [16*]. Further validation on these RFC1-related disorders is required to confirm causal RFC1-associated pathogenicity, but it suggests a broadening phenotypic scope.
CONCLUSION: FUTURE PERSPECTIVES IN CEREBELLAR ATAXIA WITH NEUROPATHY AND VESTIBULAR AREFLEXIA SYNDROME RESEARCH

BVF involves circumscribed atrophy of the hippocampus with impairments of spatial memory and navigation [15] which would be interesting to investigate in CANVAS patients. Although sensory neuropathy is established to be a prominent feature of the disease, whether it is the site of initial disease manifestation requires further confirmation [12]. We anticipate that future work will center on identifying the mechanism underpinning the RFC1 repeat expansion. Although RFC1 pathology has been previously detailed on one CANVAS brain, further validation will be required [11**]. Additionally, no neuropathology has yet been reported on other RFC1-related disorders, which will be pivotal in understanding which phenotypes are directly caused by the RFC1 expansion. Finally, with the advancement of next-generation sequencing technology, we expect that novel genetic causes of non-RFC1 CANVAS may soon come to light, furthering mechanistic understanding and treatment options for this disease.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest