Neurological disorders caused by novel non-coding repeat expansions: clinico-genetic features and roadmap to diagnosis

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ABSTRACT

Repeat expansion disorders are an important cause of neurological disease. In recent years, the advances of the sequencing technologies, with short- and long-read genome sequencing becoming more widely available, have led to a better understanding of the role of the non-coding DNA in human diseases and has enabled the identification of several pathogenic non-coding repeat expansions in familial and sporadic cases affected by common neurological disorders with adult- and late-onset, including epilepsy, cognitive dysfunction, myopathy, neuropathy, ataxia, and movement disorders. The clinical, epidemiological, and molecular features of these recently identified non-coding repeat expansion disorders will be described in detail, to guide clinicians through their diagnosis and counselling of patients and their families.

INTRODUCTION

NON-CODING REPEAT EXPANSIONS

Repeat expansion diseases represent a heterogeneous group of conditions characterized by the expansion of short tandem repeats in the DNA (**Panel 1**). They were traditionally estimated to affect approximately 1 in 3,000 individuals(1), although their prevalence may be significantly higher(2).

Notably, the central nervous system and neuromuscular system are particularly susceptible to the detrimental effects of repeat expansions, as exemplified by polyglutamine repeat expansion diseases. These disorders, including Kennedy disease, Huntington's disease, and the most common subtypes of spino-cerebellar ataxia (SCA), have been well-known to the general neurologist for over three decades.

Recent advancements in technology have unveiled a multitude of novel pathogenic repeat expansions located within non-coding DNA regions (**Figure 1**). These expansions have been associated with various neurological syndromes, often presenting as epilepsy, cognitive dysfunction, myopathy, neuropathy, ataxia, and movement disorders. Although conditions stemming from expansions of these novel non-coding repeats are increasingly encountered in neurology practice, they are still relatively unknown to many general neurologists and clinical geneticists.

The primary objective of this review is to provide a comprehensive understanding of the clinical, epidemiological, and molecular features of the recently identified non-coding repeat expansions associated with adult- and late-onset neurological phenotypes. By doing so, we aim to provide clinicians with the knowledge required for an accurate diagnosis, management, and counselling of patients and their families.

THE DISEASES AND THEIR EPIDEMIOLOGY

Over a half of the human genome consists of non-coding repetitive elements, including tandem repeats and transposable elements(3). Tandem repeats have the highest mutational rate in the genome, a feature which has benefited human evolution, by contributing to genetic diversity and facilitating adaptation to changing environments(4), but which, on the other hand, has also been implicated in several genetic diseases(5). Indeed, expansion of tandem repeats are known to cause more than 60 monogenic disorders, most of which are primarily neurological(2).

In the last six years, the advent of long-read sequencing and the advances of bioinformatics have ushered in a new era for the identification of repeat expansions linked to various neurological and neurodegenerative conditions. This includes familial adult myoclonic epilepsy (FAME), neuronal intranuclear inclusion disease (NIID), oculopharyngodistal myopathy (OPDM), spinocerebellar ataxia type 27B (SCA27B), cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS), and X-linked dystonia parkinsonism (XDP) (**Table 1**). Notably, most of these novel repeats are located in non-coding DNA regions, a factor which initially hindered their discovery due to the limitations of previous sequencing technologies. It is also noteworthy that these recently identified non-coding repeat expansions have shown a broad geographic distribution and high prevalence, across various ethnicities, as in the case of the common SCA27B and *RFC1* CANVAS/spectrum disorder, or in specific populations (**Figure 2**), also in absence of a clear family history, underlining the urgency for general neurologists to become acquainted with them.

We will first delve into the discovery and describe the associated clinical and genetic features of recently identified non-coding repeat expansion disorders and, when known, the downstream pathogenic mechanisms. The diseases will be grouped according to the mode of inheritance (dominant, recessive, and X-linked) and, within these categories, they will be listed chronologically by the year of the discovery of the underlying genetic defect. Subsequently, we will present a practical approach to their diagnosis and management. Of note, GCA repeat expansions in the 5' untranslated region (5' UTR) of glutaminase (*GLS*) gene and GGC expansions in the 5' UTR of xylosyltransferase (*XYLT1*) gene were identified in homozygous or compound heterozygous state with a second missense or nonsense mutation in patients with glutaminase deficiency, an inborn error of metabolism leading to developmental delay and early-onset progressive ataxia, and Baratela-Scott syndrome (BSS), a rare disorder characterized by early-onset short stature, facial dysmorphisms, developmental delay, and skeletal dysplasia, respectively. However, given the focus of this review on adult- and late-onset neurological diseases they are not discussed and more detailed

information can be found elsewhere(6) . Similarly, we did not include the recently identified exonic CGG repeat expansion in *ZFHX3* associated with spinocerebellar ataxia type 4(7),(8), due to its location in coding DNA.

GENETIC AND CLINICAL FEATURES

Autosomal dominant inheritance

Familial adult myoclonic epilepsy (FAME)

Familial adult myoclonic epilepsy (FAME) also named benign adult familial myoclonus epilepsy (BAFME) or familial cortical myoclonic tremor with epilepsy (FCMTE) is a fully penetrant autosomal dominant condition with an estimated overall prevalence of less than 1:35,000 in Japan, and a possible founder effect(9). It typically manifests in adulthood although onset as early as 11 years has been reported(10). The disease is clinically characterized by distal myoclonus (cortical tremor), which resembles essential tremor and, although rare, generalized-onset seizures. Intractable seizures and mild cognitive dysfunction have been reported in few cases affected by FAME2(11). The cortical origin of myoclonus is confirmed by the presence of giant somatosensory evoked potentials, enhanced long-latency EMG reflexes, and back-averaged EEG time-locked to EMG. Complex networks engaging sensorimotor cortical and subcortical structures seem to be involved in the pathophysiology of FAME(12),.

A non-coding pentameric TTTCA repeat expansion in intron 4 of the sterile α-motif domain containing 12 (*SAMD12*) gene was identified by long-read sequencing as the cause of FAME1 in 49 Japanese families, years after the locus was initially mapped(13). The expansion occurs to the poly(A) tail of an AluSq2 retroelement and may have one of the two different two-motifs configurations, TTTTA-TTTCA and TTTTA-TTTCA-TTTTA, that range in size from 14 to 3,680 repeat units(13),(14). As opposed to TTTTA expansions, which are present in approximately 6% of healthy controls of East-Asian ancestry, no TTTCA is found, thus suggesting that the TTTCA motif drives the pathogenic process in FAME1(13). Additional rare configurations, including TTTTA-TTTGA-TTTCA(15) and TTTTA-TTTCA-TTTTA-TTTCA(16), may also lead to FAME. Repeat expansions in *SAMD12* have so far been shown to cause FAME1 in patients of Chinese, Thai, Sri Lankan, Indian and Canadian/European descent, who all share the same core ancestral haplotype(16),(17).

Following the initial discovery of TTTCA expansion causing FAME1, expansion of TTTTA-TTTCA or TTTCA motifs in different genes were identified in other FAME subtypes, including FAME2 (STARD7)(18) and FAME3 (*MARCHF6*)(19) in Caucasians, FAME4 (*YEATS2*)(20) in a Thai family, FAME6 (*TNRC6A*)(13),(21), and FAME7 (*RAPGEF2)*(13),(21) in Japanese families, and FAME8 (*RAI1*) in a Malian family(22), showing a broad locus heterogeneity. Of note the TTTCA repeat is in most cases located in the mid or terminal A-stretch of Alu elements(13).

The size of the TTTCA repeat expansion is inversely correlated with age of onset(19) and both germline instability, leading to anticipation particularly with maternal transmission, and somatic instability have been described(13).

Loss of *SAMD12* function and the accumulation of toxic RNA foci have been suggested to drive the pathogenesis in FAME1(13). Notably, RNAs containing UUUCA repeat insertion were previously shown to be toxic in spinocerebellar ataxia type 37, a distinct clinical condition which is also caused by the insertion and expansion of an intronic $TTTCA_{(31\text{-}75)}$ repeat in the 5' UTR intron 3 of DAB1(23). The identification of the same TTTCA repeat in several ubiquitously expressed genes, but remarkably distinct functions, from signal transduction (*SAMD12, RAPGEF2)*, ubiquitination (*MARCHF6),* histone acetylation (*YEATS2)*, RNAi and microRNA-induced gene silencing (*TNRC6A)* to regulation of circadian clock *(RAI1),* suggest a shared, although still unknown, repeat and tissue dependent pathogenic mechanism, at least partly unrelated with the specific function of the repeat-containing genes.

Neuronal intranuclear inclusion disease (NIID)

Neuronal intranuclear inclusion disease (NIID) is neurodegenerative disease that is pathologically characterized by the presence of intranuclear ubiquitin and p62 positive inclusions in neurons and astroglial cells. In the past, the diagnosis relied on the identification of neuronal intranuclear inclusions at post-mortem brain examination. The subsequent observation of intranuclear eosinophilic inclusions also in peripheral tissues, including the skin, has enabled an histological diagnosis of NIID while individuals are alive and has led to increased case ascertainment(24).

The onset of the disease spans from infancy to late adulthood and both familial and sporadic cases, mainly of Japanese and Chinese ancestry, have been reported. Although the clinical spectrum of NIID is wide, the syndrome is often dominated by slowly progressive cognitive decline (impaired executive function, abnormal behavior, disinhibition) together with transient encephalitic-like episodes in patients of East-Asia ancestry. Cerebellar ataxia, pyramidal involvement, muscle weakness, sensory impairment, both rest and postural tremor, parkinsonism, dysautonomia, retinopathy, and rare generalized-onset seizures are also reported in some cases(24),(25).

Brain magnetic resonance imaging (MRI) typically shows hyperintense signal of the corticomedullary junction on diffusion-weighted (DWI) imaging. Symmetric white matter T2-weighted and FLAIR hyperintensities in the frontal lobes, middle cerebellar peduncles, and in the paravermal area are also commonly observed(25).

CGG repeat expansion in the 5' UTR of the notch homolog 2 N-terminal-like protein C (*NOTCH2NLC*) was identified as the cause of NIID in over 70 sporadic and familial cases(26),(27),(28). This finding was further confirmed in a five-generation Han Chinese family. Pathogenic expansions range from 66 to 525 repeats(26,27,29). Sequence interruptions act as possible modifiers. Indeed, *NOTCH2NLC* repeats of patients with predominant weakness phenotype are particularly enriched with AGG trinucleotides(27). Other neurological conditions have been associated to *NOTCH2NLC* expansions, including essential tremor(30), Alzheimer's disease(26),(31), frontotemporal dementia(31), Parkinson's disease(26),(32), adult-onset leukoencephalopathy(33), multiple system atrophy(34), amyotrophic lateral sclerosis(35), oculopharyngodistal myopathy (OPDM)(36),(37), and, more recently, Charcot-Marie-Tooth disease(38). Notably, *NOTCH2NLC* expansions are exceedingly rare or absent in individuals of European descent[37].

Both toxic RNA foci and repeat-associated non-ATG dependent (RAN) translation (namely, a form of non-canonical translation initiated at an expanded repeat RNA in the absence of an ATG start codon) of polyglycine peptides, which form toxic intranuclear aggregates, have been observed in NIID(39),(40). The gain of function mechanism of RNA and repeat peptides in NIID parallels previous observations in fragile X-associated tremor/ataxia syndrome, a disorder also caused by $CGG_{(55\text{-}200)}$ repeat expansion in the 5' UTR of *FMR1*(41). Interestingly, there appears to be a pathogenic expansion "range" rather than a simple "threshold" associated with CGG or CCG expansions, which is different from most other repeat expansion diseases for which a linear relationship between repeat size and AOO is usually observed. Indeed, very large CGG expansions typically lead to gene silencing through DNA methylation and chromatin remodelling, which is detrimental in hemizygous state in *FMR1* (fragile X syndrome), but appear to be tolerated in autosomal genes associated with NIID and OPDM, counteracting the toxic effect of repeat RNA and/or peptides(26–29).

Oculopharyngodistal myopathy (OPDM)

OPDM was first described in 1977 in four families with an autosomal dominant pedigree. It is a rare, adult-onset disease, characterized by progressive ptosis, external ophthalmoplegia, facial weakness, swallowing difficulties, and distal predominant limb weakness. Although most cases were reported from Japan and China, a few families and sporadic cases were also described in other regions, including Turkey and Europe(42).

Muscle biopsy typically reveals chronic myopathic changes including rimmed vacuoles and intranuclear filamentous inclusions, which are also evident in skin biopsy.

To date, heterozygous CGG or CCG repeat expansions in the 5' UTR of four different genes have been identified in Japanese and Chinese patients affected by OPDM including CGG expansions in *LRP12*

(OPDM1)(26), *GIPC1* (OPDM2)(43),(44), *NOTCH2NLC* (OPDM3)(36),(37), and CCG • GGC (from antisense transcription) expansion in *RILPL1* (OPDM4)(45),(46). Non-muscle features, including leukodystrophy, peripheral neuropathy, and other neurological manifestations have been reported in patients with OPDM3(37). Also, CGG • CCG repeat expansions in *LOC642361/NUTM2B-AS1*(26) were identified in a Japanese family with oculopharyngeal myopathy and leukoencephalopathy (OPML), thus supporting the existence of a broad phenotypic spectrum of CGG related disease. More recently, a novel heterozygous CCG repeat expansion has been identified in the 5' UTR of *ABCD3* gene (OPDM5) among Caucasians(47).

Similarly to NIID, in OPDM there seems to be an interval of pathogenic expansion between 85-289 CGG (LRP12), while both smaller and very larger expansions are tolerated.

Notably, as also observed in FAME, the identification of CGG or CCG repeats underlying OPDM in several ubiquitously expressed genes involved in diverse cellular processes from signalling (*LRP12, NOTCH2NLC*), scaffolding (*GIPC1*), protein transport and regulation of cell shape and polarity (*RILPL1*) to peroxisome biogenesis (*ABCD3*), suggests that the pathogenic mechanism could be at least partly independent of the repeat-containing genes but may be rather caused by repeat-dependent toxicity in susceptible muscle tissue. Indeed, although the exact disease causing mechanism of OPDM remains largely unknown, RNA-mediated toxicity and protein toxicity (poly-glycine peptides) due to RAN translation have been hypothesized to play a role in the myodegeneration of OPDM(37),(39),(43),(45),(46).

Late-onset spinocerebellar ataxia type 27B

The spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal dominantly inherited disorders characterized by progressive degeneration of cerebellum, which can be isolated or complex, with pyramidal, extrapyramidal, cognitive, peripheral nerve, or retinal involvement. SCAs are mainly caused by repeat expansions of CAG unit located in the coding regions of multiple genes which lead to the incorporation of long and aggregate-prone polyglutamine stretches in the open reading frame of the corresponding repeat containing genes. Nonetheless, until recently, a large proportion of patients with isolated cerebellar ataxia remained undiagnosed.

TTC (AAG, in genomic + strand coordinates) repeat expansions in intron 1 of fibroblast growth factor 14 (*FGF14*) were recently identified as a common cause of mostly isolated late-onset cerebellar ataxia. Since point mutations in *FGF14* were already known to cause a form of spinocerebellar ataxia, namely SCA27A, the novel disease entity associated with repeat expansion in the same gene was termed SCA27B(48),(49).

FGF14 expansions were shown to account for 10 to 61% of unsolved cases of late-onset ataxia in ethnically diverse cohorts(48–52). Repeat expansions of at least 250 TTC repeats are deemed pathogenic, although $TTC_{(250\text{-}300)}$ expansions appear to be incompletely penetrant(48),(49). Notably, expansions of non-pure TTC motifs, including TTCTCC (AAGAGG), appear to be nonpathogenic(48),(52) , although their size may be similar or larger compared to pathogenic uninterrupted TTC expansions. Almost a third of patients with SCA27B present sporadically, reflecting the high degree of intergenerational instability of the *FGF14* repeat locus(53).

Patients typically present with a slowly progressive pan-cerebellar syndrome that is frequently associated with cerebellar oculomotor signs(54). The disease begins on average between the age of 50 and 70 years. The age of onset only weakly correlates negatively with the size of the repeat expansion. Nearly half of the patients experience episodic symptoms at disease onset, which may include diplopia, vertigo, dysarthria, and ataxia. Alcohol intake and exercise are commonly reported triggers. Downbeat nystagmus is observed in 42% of patients, while visual disturbances, such as oscillopsia, diplopia, and visual blurring, are reported by 48% of them(48). Additional features may include postural tremor, vestibular hypofunction, pyramidal signs, and autonomic dysfunction. Some patients display a mild axonal peripheral sensory or sensorimotor neuropathy(51),(55).

Brain MRI may show mild to moderate cerebellar atrophy which is most pronounced in the vermis. Neuropathological examinations have confirmed the predominant vermian atrophy and detected loss of cerebellar Purkinje and granule cells, and gliosis of the molecular layer.

The intronic repeat expansion in SCA27B, which recognizes the similar repeat motif also found in Friedreich ataxia (TTC in *FGF14*-SCA27B and AAG in *FXN*-Friedreich ataxia, in sense transcript coordinates),

is thought to cause loss-of-function by interfering with *FGF14* transcription. Preliminary studies in patient-derived post-mortem cerebellum and induced pluripotent stem-cell-derived motor neurons have shown reduction of *FGF14* RNA and protein levels in patients compared to controls(48).

Autosomal recessive inheritance

Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS)

The first clinical description of the cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) as an entity dates back to the 1990s, but its genetic cause remained unknown until recently(56),(57).

Patients typically present in their fifties with imbalance, which worsens in absence of visual guidance. Sensory symptoms and signs appear before the onset of overt ataxia. Muscle bulk, tone and power are typically preserved. Knee and upper limb reflexes are most often normal or brisk while ankle reflexes are frequently reduced to absent(58),(59),(60). Approximately one-third of patients may report head-movement induced oscillopsia(58),(60), while others have subclinical involvement of the vestibular system(58). Cerebellar oculomotor signs, such as gaze-evoked nystagmus, saccadic pursuit, and dysmetric saccades, are also identified in more than a half of patients, years before subjective complaints of dysarthria and dysphagia. A spasmodic dry cough is fairly typical and it can precede the neurological onset by up to three decades(58),(60). Autonomic dysfunction is observed in up to a third of patients, although seldom disabling(58),(60) . Motor neuron involvement(61), parkinsonism(62),(63), and cognitive impairment(64) have been described in few patients.

Nerve conduction studies show in all patients widespread reduction or absence of sensory nerve action potentials while motor conduction studies are typically normal. Brain MRI may show cerebellar atrophy predominant in the vermis later in the disease course, and vestibular testing often reveals the presence of bilateral vestibular impairment, nonetheless both investigations may be initially normal. Few neuropathological studies have demonstrated moderate loss of Purkinje and granule cells mainly affecting the vermis together with a diffuse neuronal loss in the dorsal roots, trigeminal, and vestibular ganglia(65),(66).

Linkage analysis and whole genome sequencing in multiple families identified biallelic pentanucleotide TTCCC (AAGGG in genomic + strand coordinates) repeat expansions in intron 2 of replication factor C subunit 1 (*RFC1*) as the cause of CANVAS and a frequent cause of late-onset ataxia. The TTCCC maps to the poly(A) tail of an AluSx3 retroelement and differs in terms of both size and nucleotide sequence from the $TTTTC_{(11)}$ microsatellite (*i.e.*, containing 11 TTTTC pentanucleotide repeat units), which represents the normal reference in the human genome. Indeed, the pathogenic repeat size usually ranges between 250-2,000 TTCCC repeat units(56).

Rarer pathogenic expansion motifs have been described in specific populations, namely two motifs TTTCC-TTCCC (AAAGG-AAGGG), in the New Zealand and Cook Island Māori population(67), and TGTCC (ACAGG) in Asian-Pacific and Japanese patients(68). More recently additional pathogenic motifs including large TTTCC (AAAGG), TCCCG (AGGGC) and two-motif TTCCG-TTCCC (AAGGC-AAGGG) and TTTCC-TTCCC (AAAGG-AAGGG) expansions were identified in Caucasians, thus indicating that the size and GC content of repeats may be more important than the exact repeat motif(69). Notably, the allele frequency of the common TTCCC expansions nears 4% in different populations, suggesting that *RFC1* expansion may represent one of the most common recessively inherited neurodegenerative conditions(56). This is supported by the identification of biallelic *RFC1* expansion in over 30% of patients with chronic sensory axonal neuropathy(70),(71), a common condition in the elderly population that is generally considered idiopathic(72) or, in some cases, inflammatory.

To date, the mechanism underlying neurodegeneration in *RFC1* expansion remains elusive. No change in *RFC1* mRNA and protein levels was observed in patients' lymphoblasts and fibroblasts, muscle, and post-mortem brain tissue. Moreover, no RNA foci were identified in the cerebellum of one post-mortem case(56). While complete loss of RFC1 appears incompatible with life, the recent identification of patients carrying heterozygous TTCCC expansion *in trans* with a null variant in *RFC1*, leading to decreased

mRNA and protein levels, supports the existence of a possible underlying loss-of-function mechanism(73–75).

X-linked inheritance

X-linked dystonia parkinsonism (XDP)

X-linked dystonia parkinsonism (XDP; Lubag syndrome, formerly DYT3) is a neurodegenerative disorder that has hitherto been recognized primarily in males with ancestry traced to Panay Island in the Philippines due to a presumed founder effect in this population. In males, the average age of onset is 40 years and that of death is 56 years(76). The disease begins most often with focal dystonia, commonly in the legs, which progresses to generalized dystonia, and is associated with parkinsonism(76). However, there is evidence that some patients with XDP may exhibit isolated resting and/or postural tremor or parkinsonism at onset(76). Additional features include dysarthria, dysphagia, and cognitive impairment. Heterozygous female carriers usually do not develop the full syndrome, though some may show non-progressive focal dystonia with parkinsonism, albeit milder than that in males(77)

A pathogenic intronic ~2.6 kb fragment, comprising a short interspersed nuclear element (SINE), a variable number of tandem repeat (VNTR), and an Alu element, together named SINE-VNTR-Alu (SVA), is inserted in intron 32 of TATA-binding protein (TBP)-associated factor-1 (*TAF1*) in all individuals with XDP(78–80). The VNTR is an a hexameric AGAGGG repeat expansion of 35-52 repeats, the length of which is polymorphic among XDP patients and inversely correlates with age of onset(78–81). Indeed, the AGAGGG expansion appears to be the primary underlying cause of XDP, although a possible participation of other elements of the SVA cannot be excluded.

To date, few studies of postmortem brain tissue from XDP cases were performed and have shown atrophy of the neostriatum due to a loss of striosomal medium spiny neurons(82). Basal ganglia atrophy, starting from the anterior and medial putamen, and iron accumulation were shown to predate the clinical onset of XDP(83). Furthermore, neuroimaging studies have documented volume loss and functional abnormalities across multiple brain regions(84), which may be consistent with the widespread expression of *TAF1* throughout the central nervous system (CNS)(85).

TAF1 encodes a component of the transcription factor II D complex that mediates transcription by RNA polymerase II(86). Transcriptomic analyses of XDP human cell models exhibit three defects in *TAF1* expression: aberrant RNA splicing, increased partial retention of intron 32, and decreased transcription of 3' exons that reduces levels of the full-length transcript. All of these transcriptional defects were rescued by CRISPR-based excision of the SINE-VNTR-Alu element(80). Therefore a partial loss-of-function of *TAF1* due to the intronic repeat expansion itself has been hypothesized as primary mechanism underlying XDP neurodegeneration(78),(80). Nonetheless, additional mechanisms may be at play since missense variants in *TAF1* are known to be associated with intellectual disability(87), but not parkinsonism or dystonia, while complete loss of *TAF1* is not compatible with life.

DIFFERENTIAL DIAGNOSIS

We will now discuss the clinical impact of the identification of these novel and frequent non-coding repeats and how their suspicion and, when appropriate, genetic testing (**Panel 2**), should be incorporated in the clinical reasoning and diagnostic work-up of patients presenting with common neurological complaints (**Appendix 1**).

Myoclonus and epilepsy

Myoclonus is a hyperkinetic movement disorder which presents with sudden, brief, involuntary muscle jerks. The initial diagnostic approach is usually guided by the underlying physiology. Indeed, myoclonus can be generated in the cortex, subcortex, in the spinal cord, or in the peripheral nerves(88).

After exclusion of reversible and secondary causes of myoclonus (e.g., liver and renal failure, electrolyte, and acid-alkaline disturbances), FAME should be suspected in patients presenting with adult-onset distal action- and posture-induced myoclonus, predominantly affecting the upper limbs, and usually

exaggerated by sleep deprivation and/or photostimulation, often in the presence of a dominant family history. Generalized-onset seizures with good response to antiepileptic medication are rarely associated and their absence does not rule out the disease(10). Notably, FAME can be differentiated from progressive myoclonic epilepsies thanks to its and typically non-progressive disease course and the absence of cognitive decline. However, Intractable seizures and mild cognitive dysfunction have been reported in few cases affected by FAME2(11).

FAME should also be distinguished from essential tremor. As opposed to essential tremor, the cortical tremor of FAME is more irregular and jerkier. Also, while alcohol intake might improve essential tremor, it usually worsens cortical tremor and should be avoided(89) (**Appendix 1**). Despite the unifying pathogenic TTTCA repeat motif, a broad genetic heterogeneity underlies FAME, since expansions in *SAMD12*, *YEATS2*, *TNRC6A*, and *RAPGEF2* are typically found in patients from East-Asia (except for one reported family of Canadian/European descent with TTTCA expansion in *SAMD12*(16)), while expansions in *STARD7* and *MARCHF6* are identified in patients of European descent, and, although based on a single family observation, RAI1 expansion are found in Africans.

Cognitive decline and encephalitic-like episodes

NIID is a neurodegenerative condition which is almost exclusively observed in patients of East-Asian ancestry. The disease typically presents with cognitive decline due to frontal lobe dysfunction, and encephalitic-like episodes. A dominant family history, if present, may further orient the diagnostic work-up but it is not necessary for its diagnosis.

Routine laboratory testing, brain MRI, and CSF examination are recommended to rule out other causes of dementia and/or consciousness impairment, including acquired and genetic leukoencephalopathies and leukodystrophies (**Appendix 1**). In NIID brain MRI usually shows a high-intensity signal on DWI in the corticomedullary junction, and T2-weighted hyperintensity in the middle cerebellar peduncles. Elevated proteins, up to approximately 1g/ml, can be observed on CSF examination(24). When performed, the identification of ubiquitin- and p62-positive intranuclear inclusions on skin biopsy can further strengthen its suspicion.

The definite diagnosis of NIID relies on the identification of CGG repeat expansions in *NOTCH2NLC*.

Oculopharyngeal and distal limb weakness

Patients with OPDM present with onset of ptosis usually in the 2nd decade followed by external ophthalmoplegia, facial weakness, bulbar involvement, distal limb weakness and atrophy. A dominant family history may be present although many cases are sporadic(42).

Needle EMG can be performed to confirm the myopathic nature of this condition. Muscle biopsy is also recommended since it usually reveals chronic myopathic changes with rimmed vacuoles. Also, ubiquitin- or p62-positive intranuclear or cytoplasmic inclusions are rarely observed.

OPDM shares some clinical similarities with oculopharyngeal muscular dystrophy, a condition caused by $GCG_{(8-13)}$ expansion in *PABPN1*, including facial weakness with ptosis and dysphagia. However, compared to OPMD, there is an earlier onset (3rd - 5th decade), ophthalmoplegia is more frequently observed and more severe(45), and limb weakness predominates distally. Other key differential diagnoses of OPDM include chronic progressive external ophthalmoplegia, different myopathies with distal predominant weakness, and congenital myasthenic syndromes (**Appendix 1**).

Patients from East-Asia with OPDM should be screened for the presence of CGG or CCG expansions in *LRP12*, *GIPC1*, *NOTCH2NLC*, *RILPL1*, and *LOC642361,* while in individuals of European descent testing for CCG expansions in *ABCD3* gene is recommended.

Late-onset ataxia and sensory neuropathy

Ataxia can be caused by the impairment of the cerebellum and the spino-cerebellar pathways, the sensory nerves and/or the posterior columns, and the vestibular system. Medical history and examination generally help to differentiate its origin. Brain and spine MRI, nerve conduction studies and, where

available, vestibular testing, should be performed in all cases for a precise diagnosis and to streamline investigations and genetic testing. The diagnostic approach to late-onset ataxia needs to account for acquired (vascular, neoplasm, inflammatory, toxic-metabolic), degenerative (multisystem atrophy) and genetic causes(90).

Genetic testing is indicated if the initial investigations are unrevealing, and the presentation is consistent with a slowly progressive condition. Clinical features and pattern of inheritance should guide the genetic work-up. While the common spinocerebellar ataxia (SCA1,2,3,6,7), Friedreich's ataxia, spastic paraplegia 7, and fragile X-associated tremor/ataxia syndrome are routinely tested for, they individually account for a small proportion of late-onset ataxia cases.

All patients with late-onset ataxia and clinical and/or neurophysiologic evidence of sensory neuropathy should be tested for biallelic *RFC1* expansion. *RFC1* test should also be considered early in the diagnostic workup of an isolated sensory neuropathy/neuronopathy without overt ataxia, in order to avoid misdiagnosis and, potentially, unnecessary immunosuppressive treatments (**Panel 3**)(70),(71). The report of chronic cough, and the identification of vestibular areflexia further increase the likelihood of a positive *RFC1* test. Conversely, *RFC1* expansion are very rare to absent in cases with isolated cerebellar involvement without sensory neuropathy(91). *RFC1* disease should be differentiated from late-onset Friedreich's ataxia and mitochondrial diseases, including sensory ataxic neuropathy, dysarthria, and ophtalmoparesis (SANDO) caused by biallelic variants in the DNA polymerase gamma, catalytic subunit (POLG) gene, and neuropathy, ataxia, and retinitis pigmentosa (NARP) caused by pathogenic variants in the mitochondrially encoded ATP synthase membrane subunit 6 (MT-ATP6) gene.

Conversely, patients with a slowly progressive pan-cerebellar syndrome should undergo testing for *FGF14* expansions. Early episodic symptoms and a dominant family history may also serve to discriminate SCA27B from *RFC1*-related disease, although in some families carrying *RFC1* expansion a pseudo-dominant inheritance can be encountered. On the other end, SCA27B should be distinguished from episodic ataxias, especially episodic ataxia type 2, and adult-onset spinocerebellar ataxias presenting with a rather pure cerebellar phenotype, such as SCA5, SCA6, SCA8, and SCA45 (**Appendix 1**). Importantly, both *RFC1* and *FGF14* should be considered in the differential diagnosis of multiple system atrophy (MSA).

Dystonia and parkinsonism

Dystonia with parkinsonism encompasses a combination of dystonia – a hyperkinetic movement disorder which causes abnormal, often repetitive movements, postures, or both *plus* parkinsonism which associates bradykinesia with either rest tremor, rigidity, or both.

The diagnostic work-up of patients with dystonia-parkinsonism starts with careful phenotyping of the movement disorder. Age, type and tempo of onset, body distribution, temporal pattern of dystonia, presence of other associated features, family history, and levodopa responsiveness are essential clues to guide the diagnostic process.

After considering acquired and potentially treatable conditions, including exposure to dopamine receptor blocking medications, and if the preliminary laboratory and imaging do not point to a secondary cause, a genetic origin should be considered. The differential diagnoses should include dopamine pathway disorders, inborn errors of metabolism, diseases related to brain metal overload, and recessive/dominant parkinsonisms (**Appendix 1**), particularly in cases with family history, early onset, or if the clinical phenotype is suggestive(92). XDP testing should be considered in all male patients of Filipino ancestry over the age of 40 presenting with dystonia, parkinsonism, or a combination of both.

CONCLUSIONS AND FUTURE DIRECTIONS

In the last years, the wider use of short and long-read whole-genome sequencing has fostered the identification of many novel repeat expansions causing neurological disease(93). Because of their widespread occurrence, it is essential that neurologists and geneticists become familiar with the clinical features and molecular causes of these recently described disorders. Indeed, their frequency appears high worldwide across different ethnicities (*RFC1* CANVAS/spectrum disorder, SCA27B), or in some specific

populations (FAME, NIID, OPDM in East Asians and XDP in Filipino males). Importantly, with the exception of FAME which typically manifests in families, they often present sporadically, either because of the recessive mode of inheritance (e.g., *RFC1* CANVAS/spectrum disorder) or highly variable penetrance (up to a third of cases with SCA27B, NIID, and OPDM are sporadic), so that absence of family history should not discourage clinicians to suspect them.

Their recent recognition has provided further evidence of how non-coding repeat expansion diseases, which also include previously identified fragile X syndrome/fragile X-associated tremor/ataxia syndrome, myotonic dystrophy, *C9orf72* amyotrophic lateral sclerosis, and frontotemporal degeneration and additional subtypes of SCA, exhibit molecular and clinical features which differ from coding repeat expansion diseases, including the well-known polyglutamine repeat expansion diseases (**Table 2**)(1),(6),(94),(95) .

Although specific diagnostic tests for most of these newly identified conditions are still not widely available there is intense research to develop more sensitive and accurate genetic testing techniques from short- and long-read whole genome sequencing(96),(97). In particular, the gradual adoption in genetic labs of long-read sequencing technologies, which provide a more even coverage of these repetitive regions, will lead to increased identification of these mutations, further reducing the diagnostic gap in several common and rare Mendelian diseases.

Unfortunately, for all the conditions here listed there is no specific therapy, hence current management relies on symptomatic treatments. In FAME the treatment is aimed at controlling cortical myoclonus, while in NIID the prevention of concurrent illness is key to avoid encephalitic-like episodes. Both in OPDM and late-onset ataxia, physical and occupational therapy are aimed at preserving functional performances together with bulbar and/or respiratory complications. Treatment of pain and cough in *RFC1* CANVAS/spectrum disorder and downbeat nystagmus/ataxic symptoms in SCA27B, respectively should be also looked for. In XDP treatment is aimed at improving focal dystonia and parkinsonism. For more details see **Appendix 2**.

Current research efforts are aimed at building international networks to better track the natural history of these conditions and identify sensitive biomarkers which could aid in diagnosis, disease monitoring, and assessing treatment efficacy(98). Genome-wide studies of genetic modifiers of disease onset and progression also represent a powerful tool to harness naturally occurring genetic variation to unravel pathways relevant to their pathogenesis, e.g. DNA damage and repair, and identify potentially druggable targets(99).

Although their management remains still largely symptomatic, we are hopeful that ongoing investigations on the mechanisms by which non-coding repeat expansions cause neurodegeneration will lead to the development of effective therapies, including promising approaches through CRISPR-Cas9 gene editing, small molecule therapies, and antisense oligonucleotides (ASOs), in the near future(100).

SEARCH STRATEGY AND SELECTION CRITERIA

References included in this review were identified by searches on PudMed between December 1, 2017, and February 29, 2024, and from the references of relevant articles. The main search terms have been: “repeat expansion disorder/disease”, “non-coding DNA”, “Alu element”, “microsatellite”, “tandem repeat”, “next-generation sequencing”, “NGS”, “whole genome sequencing”, “WGS”, “long-read”, “ataxia”, “sensory neuropathy/neuronopathy”, “cerebellar ataxia neuropathy and vestibular areflexia syndrome”, “CANVAS”, “RFC1”, “FGF14”, “familial adult myoclonus epilepsy”, “FAME”, “X-linked dystonia parkinsonism”, “XDP”, “neuronal intranuclear inclusion disease”, “NIID”, “oculopharyngodistal myopathy”, “OPDM”, “SCA27B”. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this review.

Panel 1. Glossary of terms

Polyglutamine (polyQ) repeat expansion diseases: group of genetic disorders characterized by the expansion beyond a certain threshold of CAG nucleotide triplet (which codes for the amino acid

Panel 2. Genetic testing of repeat expansions

PCR based approaches including repeat-primed PCR (RP-PCR) and sizing PCR

- Detection of expansions of known repeat motif
- Cost-effective and available in many diagnostic labs
- Targeted tests (a single repeat locus and motif can be tested at one time)
- PCR fails to amplify large expansions and/or with high GC content (e.g., *RFC1*) and alternative methods, including Southern blotting, are required for their sizing

Whole-exome sequencing (WES)

- Unable to detect most non-coding repeat expansions because of their location (introns) or high GC content (CGG expansion in 5' UTR)

Short-read whole-genome sequencing (WGS)

- High sensitivity and specificity for exonic CAG repeat expansions(93)
- It allows genome-wide profiling of all short-tandem repeats, along with single nucleotide variants and small structural variants
- Because the read length (~150 nucleotides) is often shorter compared to the repeat expansion, short-read whole-genome sequencing is unable to accurately determine the exact repeat size and motif of large non-coding repeats
- Variable accuracy of bioinformatic tools (e.g., Expansion Hunter) in predicting size and sequence content of non-coding repeat expansions(106)

Long-read WGS

- It provides reliable information about repeat size and motifs at genome-wide level(96),(107), along with single nucleotide variants, structural variants, and their phasing
- High cost and limited availability in genetic labs
- Targeted enrichment methods (Crispr/Cas9, Read-Until, PCR-based) are available but show variable sequencing yield and accuracy depending on specific repeat size and sequence(69),(96)

Non-sequencing based optical genome mapping (OGM)

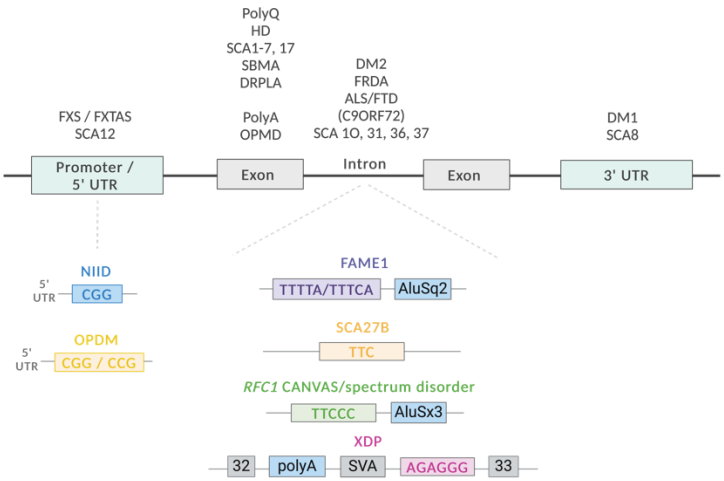
- Accurate assessment of all structural variants, including large repeat expansions (>500 nucleotides)(101) at genome-wide level
- It does not provide information on repeat motifs (e.g., it cannot distinguish between some non-pathogenic and pathogenic motifs, TTTTA *vs* TTTCA in FAME, or TTTTC *vs* TTCCC in *RFC1* CANVAS/spectrum disorder, respectively)
- It has a lower accuracy for the detection of repeat expansions below the threshold of ~500 nucleotides

Panel 3. A case study

We describe the case of a female who initially presented in her 40s with acute burning dysesthesia in her hands and feet, followed by numbness extending to her extremities. There was no family history of neurological disease or consanguinity. Clinical examination and nerve conduction studies indicated a length-dependent, axonal, sensory neuropathy. A routine laboratory screening for acquired causes of neuropathy was negative. Simultaneously, she complained of dry eyes, dry throat, and chronic cough. A lip biopsy revealed mild lymphocytic and plasma cell infiltration, while ENA (extractable nuclear antigen) antibodies were negative. The patient received a diagnosis of Sjogren-related inflammatory sensory neuropathy and was treated with hydroxychloroquine. However, the disease progressed and led to gait impairment. Ten years later, *RFC1* testing was initiated, revealing the presence of biallelic pathogenic AAGGG expansions. Importantly, there was no involvement of the cerebellum or vestibular system.

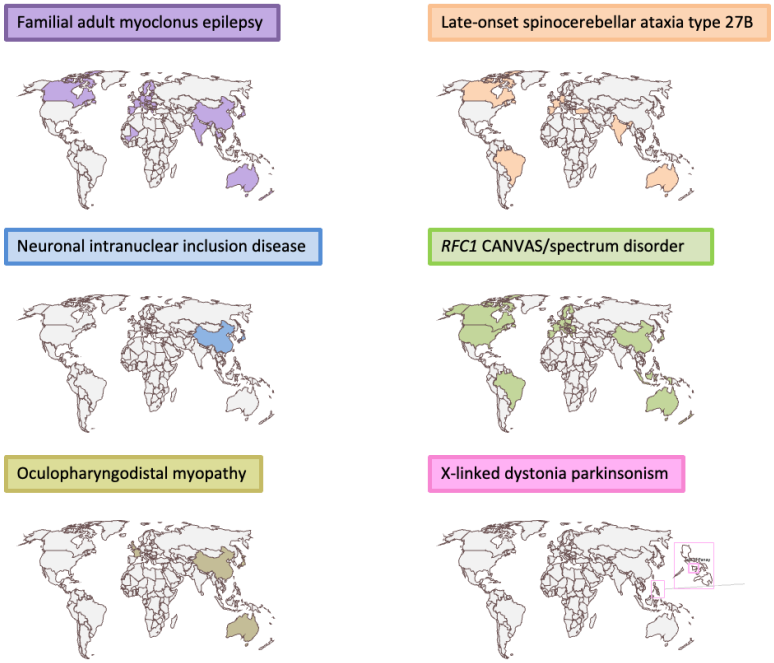
RFC1 expansions are a common cause of sensory neuropathy with cough. In this case it is likely that the Sjogren's diagnosis was incorrect or coincidental(108) and played no or limited impact on the neuropathy. This is important considering potential unnecessary use of immunosuppressive therapies.

Figure 1. Genomic location of recently identified non-coding repeat expansions causing neurological diseases



The expanded satellites are shown below the corresponding location with matching colours throughout the text: XDP (pink), FAME (violet), RFC1 CANVAS/spectrum disorder (green), NIID (light blue), OPDM (ochre), SCA27B (orange). Representative examples of known repeat expansion disorders are shown in grey above the corresponding location.

Figure 2. Geographical distribution



ALS/FTD: amyotrophic lateral sclerosis/frontotemporal dementia; FAME: familial adult myoclonus epilepsy; CANVAS: cerebellar ataxia neuropathy vestibular areflexia syndrome; DM: myotonic dystrophy; DRPLA: dentatorubral pallidoluysian atrophy; FRDA: Friedreich's ataxia; FXS: fragile X syndrome; FXTAS: fragile X-associated tremor/ataxia syndrome; HD: Huntington disease; NIID: neuronal intranuclear inclusion disease; OPDM: oculopharyngodistal myopathy; OPMD: oculopharyngeal muscular dystrophy; PolyA: polyglycine; PolyQ: polyglutamine; RFC1: replication factor C subunit 1; SBMA: spinal bulbar muscular atrophy; SCA: spinocerebellar ataxia; SVA: SINE (short interspersed nuclear element)-VNTR (variable nuclear tandem repeat)-Alu; UTR: untranslated region; XDP: X-linked dystonia parkinsonism.

Table 1. Neurological disorders caused by novel non-coding repeat expansions

Disorder	Gene genomic location (GRCh38/hg38)	Location in gene	Reference motif Gene coordinates (genomic coordinates)	Reference size Number of repeat units	Pathogenic repeat motif Transcript sense (+ strand)	Pathogenic repeat size Number of repeat units	Pathogenic mechanism	Ethnic / geographic distribution	Main clinical features	References
Autosomal dominant										
FAME1[$]	*SAMD12* chr8:118366813-118366918	Intron	TTTTA (AAAAT)	7-13	TTTCA (TGAAA)	14-3,680	RNA-mediated toxicity (RNA foci)	East-Asian	Cortical tremor, seizures with generalized motor (tonic-clonic) onset	(13),(14)
FAME2	*STARD7* chr2:96197067-96197124	Intron	TTTTA (AAAAT)	12	TTTCA (TGAAA)	150-460	Unknown	European		(18)
FAME3	*MARCHF6* chr5:10356339-10356411	Intron	TTTTA (TTTTA)	9-20	TTTCA (TTTCA)	668-2,814	Somatic genomic rearrangements (if expansion >10 kb)	European		(19)
FAME4	*YEATS2* chr3:183712177-183712226	Intron	TTTTA (TTTTA)	7	TTTCA (TTTCA)	962-1,262	Unknown	East-Asian		(20)
FAME6	*TNRC6A* chr16:24613439-24613532	Intron	TTTTA (TTTTA)	18	TTTCA (TTTCA)	27-29	Unknown	East-Asian		(13)
FAME7	*RAPGEF2* chr4:159342527-159342618	Intron	TTTTA (TTTTA)	5-12	TTTCA (TTTCA)	4-19	Unknown	East-Asian		(13)
FAME8	*RAI1* chr17:17808359-17808460	intron	TTTTA (TTTTA)	16-22	TTTCA (TTTCA)	9–334	Unchanged *RAI1* expression, haploinsufficiency unlikely	African (single large family from Mali)		(22)
NIID	*NOTCH2NLC* chr1:149390803-149390842	5′ untranslated region	CGG (CGG)	5-39	CGG (CGG)	66-525	RNA-mediated toxicity (RNA foci), toxic polyG peptides (RAN translation[§])	East-Asian	Cognitive dysfunction, psychosis, parkinsonism, muscle weakness, sensory disturbances, pyramidal and cerebellar signs	(26–29)
OPDM1	*LRP12* chr8:104588973-104588999	5′ untranslated region	CGG (CCG)	9-13	CGG (CCG)	85-289	Unknown	East-Asian	Ptosis, external ophthalmoplegia, facial weakness, pharyngeal and distal limb weakness	(26)
OPDM2	*GIPC1* chr19:14496042-14496085	5′ untranslated region	CGG (CCG)	6-31	CGG (CCG)	73-164	Unknown	East-Asian		(43),(44)
OPDM3	*NOTCH2NLC* chr1:149390803-149390842	5′ untranslated region	CGG (CGG)	6-26	CGG (CGG)	83-674	Unknown	East-Asian		(36),(37)
OPDM4	*RILPL1* chr12:123533721-123533755	5′ untranslated region/ promoter	CCG • CGG[&] (CGG)	12-40	CCG • CGG[&] (CGG)	135-197	RNA-mediated toxicity (RNA foci), toxic polyG peptides (RAN translation), bidirectional transcription	East-Asian		(45),(46)
OPDM5	*ABCD3* chr1: 94418389-94518666	5′ untranslated region	CCG (CGG)	7	CCG (CGG)	118-694	Increased expression of repeat containing ABCD3 transcript	European		(47)

OPML1	*LOC642361/ NUTM2BAS1* chr10:79826386-79826403	Long non-coding RNA	CGG • CCG[&] (CGG)	6	CGG • CCG[&] (CGG)	~700	Unknown	East-Asian	OPDM and white matter abnormalities	(26)
SCA27B	*FGF14* chr13: 102161575-102161726	Intron	TTC (AAG)	50	TTC (AAG)	≥250	Haploinsufficiency	Different ethnicities	Cerebellar ataxia, downbeat nystagmus, episodic symptoms	(48),(49)
Autosomal recessive										
***RFC1* CANVAS/ spectrum disorder**	*RFC1* chr4:39348425-39348483	Intron	TTTTC (AAAAG)*	11	TTCCC (AAGGG)*	250-2,000	Unknown	Different ethnicities	Sensory disturbances, imbalance, oscillopsia, chronic dry cough, dysarthria and dysphagia	(56)
X-linked										
XDP	*TAF1* chrX:71453055-71453129	Intron (retrotransposon)	AGAGGG (AGAGGG)	4	AGAGGG (AGAGGG)	35-52	Altered splicing with intron retention, haploinsufficiency	Filipino	Focal and generalized dystonia, parkinsonism, cognitive dysfunction	(79),(80)

ABCD3: ATP binding cassette subfamily D member 3; FAME: familial adult myoclonus epilepsy; CANVAS: cerebellar ataxia neuropathy vestibular areflexia syndrome; chr: chromosome; FAME: familial adult myoclonic epilepsy; GIPC1: GIPC PDZ domain containing family member 1; LRP12: LDL receptor related protein 12; MARCHF6: membrane associated ring-CH-type finger 6; NIID: neuronal intranuclear inclusion disease; NOTCH2NLC: notch homolog 2 N-terminal-like protein C; OPDM: oculopharyngodistal myopathy; OPML: oculopharyngeal myopathy with leukoencephalopathy; RAI1: Retinoic Acid Induced 1; RAPGEF2: rap guanine nucleotide exchange factor 2; RFC1: replication factor C subunit 1; RILPL1: rab interacting lysosomal protein like 1; SAMD12: sterile alpha motif domain containing 12; SCA: spinocerebellar ataxia; STARD7: stAR related lipid transfer domain containing 7; TAF1: TATA-binding protein (TBP)-associated factor-1; TNRC6A: trinucleotide repeat containing adaptor 6A; XDP: X-linked dystonia parkinsonism; XYLT1: xylosyltransferase; YEATS2: YEATS domain containing 2.

Short tandem repeats are indicated according to genomic coordinates. Pathogenic repeat motifs are indicated according to the sense strand/genomic coordinates in case of genes located on + strand or sense strand (genomic coordinates) in case of genes located on - strand.

[$] FAME is also known as benign adult familial myoclonic epilepsy (BAFME), familial cortical myoclonic tremor with epilepsy (FCMTE), or autosomal dominant cortical myoclonus and epilepsy (ADCME). Same numbering as FAME1-7 is used.

*Please note that FAME5 (1q31.3-q32.2) is not reported in **Table 1** since it is not caused by a repeat expansion but a biallelic single base pair deletion in contactin-2 (CNTN2) gene.*

**Additional rare pathogenic motifs are discussed in the text.*

[§]Repeat-associated non-ATG (RAN) translation is a form of non-canonical translation initiated at an expanded repeat RNA in the absence of an ATG start codon.

[&]Both sense and antisense repeat containing transcripts were observed (bidirectional transcription).

Table 2. Neurological disorder caused by polyglutamine repeat expansions *vs* non-coding repeat expansions

	Polyglutamine repeat expansions	**Non-coding repeat expansions***
Genomic location	Exonic[§]	Located in non-coding DNA regions, including CGG or CCG expansion at 5' untranslated region and intronic tri-, penta- or hexanucleotide repeat expansions, flanking or part of transposable Alu elements
Pathogenic range	Depending on subtype, >30-50 repeats are typically fully pathogenic	Often large (>100, often >1000 repeats), except for some cases (e.g., XDP)
Sequence	CAG	Pathogenic repeat usually differs in terms of both size and sequence from the reference satellite (e.g., TTTCA in FAME and SCA37(23), uninterrupted TTC in SCA27B, TTCCC in *RFC1* CANVAS/spectrum disorder)
Penetrance and expressivity	Penetrance and expressivity well explained by premutation and full mutation range, which may be modulated by repeat interruptions Linear correlation between repeat expansion size, age of onset (inverse) and disease severity	Penetrance and expressivity depend on the presence of a mutated repeated unit spanning through all or part of the expanded repeat Correlation between the size of the mutant repeat insertion (rather than total expansion size) and disease severity (e.g., TTTCA size in FAME) In CGG or CCG repeat expansion diseases, existence of a pathogenic expansion "range" rather than a "threshold". While intermediate expansions lead to the toxic production of repeat RNA and/or peptides, very large expansions induce gene silencing, which is detrimental in hemizygous state in *FMR1* (fragile X syndrome), but appear to be tolerated in autosomal genes associated with NIID and OPDM
Family history	Often present. Autosomal dominant families with genetic anticipation and parent-of-origin effect	Often absent. Recessive inheritance (*RFC1* CANVAS/spectrum disorder), or dominant with highly variable penetrance and expressivity in families
Population distribution	Either widely distributed (HD), or more frequent in specific populations (SCA3, DRPLA)	The mutant repeat is often part of ancestral haplotypes, which may be frequent in specific populations (e.g., FAME, NIID, XDP) or shared across different ethnicities (e.g., *RFC1* CANVAS/spectrum disorder)
Genotype phenotype correlation	Clinical phenotype depends on both sequence of the expanded repeat and repeat-containing gene Well characterized phenotypes	Characteristic association between the repeat motif and the clinical phenotype (e.g., TTTCA in FAME, CGG or CCG in OPDM), partly independent from the repeat-containing gene Phenotype spectra are still expanding
Diagnostic testing	Accurate diagnostic genetic tests are widely available Expansions can be detected from short-read next generation sequencing (whole-genome and whole-exome sequencing)	Diagnostic tests are increasingly available, but mostly still limited to specialized Centres Expansions are not detected from whole-exome sequencing data Short-read whole-genome sequencing can be informative but fail to provide accurate sizing and analysis of repeat motif. Long-read whole-genome sequencing will likely represent the gold standard for their testing in the future

		Optical genome mapping can accurately assess all structural variants, including large repeat expansions (>500 nucleotides)(101) at genome-wide levelI, although it does not provide information on repeat motifs (e.g., it cannot distinguish between some non-pathogenic and pathogenic motifs)

*FAME: familial adult myoclonus epilepsy; CANVAS: cerebellar ataxia neuropathy vestibular areflexia syndrome; DRPLA: dentatorubral-pallidoluysian atrophy; OPDM: oculopharyngodistal myopathy; HD: Huntington disease; RFC1: replication factor C; SCA spino-cerebellar ataxia. Subunit 1; XDP: X-linked dystonia parkinsonism. *with focus on recently identified adult-onset repeats discussed in this review*.

[§]Note that not all the coding (exonic) repeats are polyglutamine stretches (e.g., polyglycine stretches in OPMD and SCA4)

Appendix 1. Roadmap to diagnosis and genetic testing

Disease	When to suspect the disease	Implication for transmission	Main differential diagnoses	Genetic testing

FAME	East-Asian (*SAMD12*, *YEATS2*, *TNRC6A*, *RAPGEF2*), Caucasian (*STARD7*, *MARCHF6*) or African (*RAI1*) ancestry
	
	Cortical tremor
	
	Rare seizures with generalized motor (tonic-clonic) onset
	
	Giant somatosensory evoked potentials and enhanced long-latency EMG reflexes
		Autosomal dominant
		
		Risk of transmission is 50%
		
		High penetrance in families is common
			Epileptic myoclonus
			- Idiopathic generalized myoclonic epilepsy
			  o Juvenile myoclonic epilepsy (Janz syndrome)
			- Progressive myoclonus epilepsies, among others
			  o Unverricht–Lundborg disease (or Baltic myoclonus)
			  o Lafora disease
			  o Myoclonus epilepsy with ragged-red fibers
			  o Neuronal ceroid lipofuscinoses
			  o Sialidosis
			
			Secondary myoclonus
			- Immune-mediated/paraneoplastic (e.g., LGI1, Caspr2, DPPX)
			- Metabolic (e.g., liver and renal failure, electrolyte and acid-alkaline disturbances)
			- Toxic/drug induced (e.g., alcohol, serotonin reuptake inhibitors)
			- Neurodegenerative (e.g., prion disease, multiple system atrophy)
			
			Essential myoclonus (myoclonus dystonia) (e.g., SGCE, ANO3)
			
			Myoclonus mimics (e.g, essential tremor syndromes)
				Diagnostic tests
				RP-PCR for pathogenic TTTCA
				Size confirmation with LR-PCR(13)
				
				Additional/research tests
				Southern-blotting(13), long-read sequencing(18–20),(102)

NIID	East-Asian ancestry Complex neurological phenotype with prominent cognitive dysfunction and encephalitic-like episodes White matter changes in the frontal lobes and cerebellar middle peduncles High-intensity signal on DWI in the corticomedullary junction	Autosomal dominant Risk of transmission is 50% High rate of sporadic presentation Reduced penetrance and	- Fragile X-associated tremor/ataxia syndrome - Oculopharyngeal myopathy with leukoencephalopathy (*LOC642361/ NUTM2B-AS1*) - Small vessel disease - Genetic leukoencephalopathies/leukodystrophies (e.g., adrenoleukodystrophy, autosomal dominant leukodystrophy - *LMNB1*, *CLCN2*, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, vanishing white matter diseases) - Toxic/metabolic (e.g., posterior reversible encephalopathy syndrome, heroin inhalation)	*Diagnostic test* RP-PCR for pathogenic CGG Size confirmation with fluorescent sizing PCR(26),(27) *Additional/research tests* Southern-blotting(26), long-read sequencing(26)

	Intranuclear eosinophilic p62 positive inclusions in skin and post-mortem brain	variable expressivity in families is common		
OPDM	East-Asian (*LRP12*, *GIPC1*, *NOTCH2NLC*, *RILP1, LOC642361 / NUTM2BAS1*) or Caucasian (*ABCD3*) ancestry Ptosis, ophthalmoplegia, dysphagia, facial and distal weakness Intranuclear eosinophilic p62 positive inclusions, rimmed vacuoles on muscle biopsy	Autosomal dominant Risk of transmission is 50% (higher risk for male-to-offspring) High rate of sporadic presentation Reduced penetrance and variable expressivity in families is common	- Oculopharyngeal muscular dystrophy - Chronic progressive ophthalmoplegia and other mitochondrial diseases - *MYH2*-related myopathy - Distal myopathies (e.g., *MYH7*, *GNE*, *DYSF*, *TTN*, *LDB3*) - Myofibrillar myopathies (e.g., *DES, CRYAB, SEPN1, BAG3, MYOT*) - Centronuclear myopathies (e.g., *MTM1, DNM2, BIN1, RYR1*) - Myotonic dystrophy type 1 - Facioscapulohumeral muscular dystrophy - Inclusion body myositis - Myasthenia gravis and congenital myasthenic syndromes	*Diagnostic test* RP-PCR for pathogenic CGG or CCG Size confirmation with fluorescent sizing PCR(26)·(36)·(37)·(43–46) *Additional/research tests* Southern-blotting(26)·(36), long-read sequencing(37)·(43–46)
SCA27B	Any patient with slowly progressive adult-onset cerebellar ataxia	Autosomal dominant High rate of sporadic presentation (~33%)	Spinocerebellar ataxia type 5, 6, 8, 37, 38, 45 Episodic ataxia type 2 Multiple system atrophy, cerebellar type - *RFC1* CANVAS/spectrum disorder	*Diagnostic test* Multi-step algorithm entailing 1. Capillary electrophoresis of fluorescent long-range PCR (*f*LR-PCR) amplification products 2. Bidirectional RP-PCRs targeting the 5'-end and 3'-end of the repeat locus 3. Gel electrophoresis of *f*LR-PCR amplification products and Sanger

				sequencing in select cases(103) *Additional/research tests* Long-read sequencing(48),(103)
***RFC1* CANVAS/spectrum disorder**	Any patient with idiopathic sensory neuropathy Adult-onset ataxia with evidence of sensory neuropathy Bilateral vestibular areflexia Chronic cough	Autosomal recessive It can be either sporadic or occurs in siblings Pseudodominant inheritance has been observed	Acquired and genetic causes of sensory neuropathies: - Immune-mediated/paraneoplastic (anti-Hu and CV2/CRMP5 antibodies) - Toxic-metabolic (e.g., platinum-based drugs) - Hereditary sensory and autonomic neuropathy (e.g., *RNF170*) Acquired and genetic causes of late-onset cerebellar ataxia - Immune-mediated/paraneoplastic - Toxic-metabolic (e.g., alcohol) - Multiple system atrophy, cerebellar type Genetic (late onset Friedreich's ataxia, sensory ataxic neuropathy, dysarthria and ophtalmoparesis (*POLG*), neuropathy, ataxia, and retinitis pigmentosa (MT-ATP6), spinocerebellar ataxia type 27B)	*Diagnostic test* Flanking PCR and RP-PCR for pathogenic TTCCC and nonpathogenic TTTCC and TTTTC motifs(58),(56) Consider full *RFC1* gene sequencing in cases with heterozygous TTCCC expansion and compatible clinical phenotype *Additional/research tests* Southern-blotting(58),(56) , long-read sequencing(69), optical genome mapping(101)
XDP	Filipino ancestry Male sex X-linked inheritance Focal or generalized dystonia Parkinsonism	X-linked Age-related penetrance (complete after ~70 years of age) Variable expressivity	Drug induced (e.g., dopamine receptor blockers) Neurodegenerative/genetic - Idiopathic or monogenic (in particular, PRKN, PINK1, DJ1, FBXO7) Parkinson's disease - Parkinson's-plus syndromes/atypical parkinsonisms - Huntington's disease (Westphal variant) - Wilson's disease - Monoamine synthesis and dopamine transport disorders - Neurodegeneration with brain iron accumulation (PANK2, WDR45, COASY, C19Orf12, PLA2G6, ATP13A2, FTL, CP) - Primary familial brain calcifications (SLC20A2, PDGFB, PDGFRB, XPR1, MYORG) Niemann-Pick type C	*Diagnostic test* PCR amplification (including long-range PCR - LR-PCR of *TAF1* SVA) followed by Sanger sequencing for the detection of single nucleotide variant haplotype markers (i.e., five disease-specific single nucleotide changes and the SVA)(79) Sizing of AGAGGG with florescent sizing PCR(79),(81) *Additional/research tests* Southern-blotting(104), long-read sequencing(79),(104),(105)

ABCD3: ATP binding cassette subfamily D member 3; ANO3: anoctamin 3; ATP13A2: ATPase cation transporting 13A2; FAME: familial adult myoclonus epilepsy; BAG3: BAG cochaperone 3; BIN1: bridging integrator 1; Caspr2: anti-contactin-associated protein-like 2; C19Orf12: chromosome 19 open reading frame 12; CANVAS: cerebellar ataxia neuropathy vestibular areflexia syndrome; CLCN2: chloride voltage-gated channel 2; CNS: central nervous system; COASY: coenzyme A synthase; CRYAB: crystallin alpha B; CV2/CRMP5: CV2/collapsin response mediator protein 5; DES: desmin; DNM2: dynamin 2; DJ1: deglycase 1; DPPX: dipeptidyl-peptidase-like protein-6; DWI: diffusion-weighted images; DYSF: dysferlin; EMG: electromyography; FBXO7: F-box only protein 7; FTL: ferritin light chain; GNE: glucosamine (UDP-N-Acetyl)-2-epimerase/N-acetylmannosamine kinase; LDB3: LIM domain binding 3; LGI1: leucine-rich, glioma inactivated 1; LMNB1: lamin-B1; MYH7: myosin heavy chain 7; MRI: magnetic resonance imaging; MT-ATP6: mitochondrially encoded ATP synthase membrane subunit 6; MTM1: myotubularin 1; MYORG: myogenesis regulating glycosidase; MYOT: myotilin; NIID: neuronal intranuclear inclusion disease; OPDM: oculopharyngodistal myopathy; PANK2: pantothenate kinase 2; PDGFB: platelet derived growth factor subunit B; PDGFRB: platelet derived growth factor receptor beta; PINK1: PTEN induced kinase 1; PLA2G6: phospholipase A2 group VI; POLG: DNA polymerase gamma; PRKN: parkin; RAI1: Retinoic Acid Induced 1; RFC1: replication factor C subunit 1; RNF170: ring finger protein 170; RYR1: ryanodine receptor; SCA: spinocerebellar ataxia; SEPN1: selenoprotein N; SGCE: sarcoglycan epsilon; SLC20A2: solute carrier family 20 member; TTN: titin; XDP: X-linked dystonia parkinsonism; WDR45: WD repeat domain 45; XPR1: xenotropic and polytropic retrovirus receptor 1.

Appendix 2. Clinical management

FAME

- Cortical myoclonus is usually treated with a combination of drugs aimed at enhancing GABAergic neurotransmission (sodium valproate, levetiracetam or piracetam, low-dose perampanel)(109)
- Although typically non progressive, the cortical tremor can gradually worsen with advanced age and a more aggressive treatment may thus be required
- Phenytoin, carbamazepine, lamotrigine, or gabapentin may paradoxically exaggerate myoclonus(109)

NIID

- Prevention of concurrent illnesses which are frequent triggers of encephalitic-like episodes
- Levodopa can be added in case of parkinsonism

OPDM

- Physical and occupational therapy aimed at preserving functional performances, and prevention of complications due to bulbar, and respiratory involvement
- Surgical treatment of ptosis and dysphagia may be considered in selected cases

Late-onset ataxia

- Regular follow-up to monitor disease progression and prevent complications (e.g., aspiration and falls)
- Physical and occupational therapy aimed at preserving ambulation and functional abilities
- In patients with *RFC1* CANVAS, tricyclic antidepressants, gabapentinoids, and serotonin and norepinephrine reuptake inhibitors may be considered in case of neuropathic pain. Also, pregabalin, amitriptyline, and morphine have shown anecdotal evidence in refractory cough. The coexistence of gastroesophageal reflux should also be excluded and treated accordingly
- 4-aminopyridine may be of benefit to treat downbeat nystagmus and ataxic symptoms in SCA27B(54)

XDP

- Intramuscular injections of botulinum toxin, alone or in combination with oral anticholinergics, and benzodiazepines may partially ameliorate focal dystonia
- Levodopa/carbidopa may improve parkisonism
- Bilateral deep brain stimulation to the internal globus pallidus has been shown to provide some relief for segmental or generalized dystonia(110)

AUTHORS' CONTRIBUTIONS

E.V.: conceptualization, data curation, writing – original draft, and writing – review & editing
H.I.: data curation, writing – review & editing
D.C.B.: data curation, writing – review & editing
D.P: data curation, writing – review & editing
F.M: data curation, writing – review & editing
R.C.: data curation, writing – review & editing
S.F.: data curation, writing – review & editing
A.T.: data curation, writing – review & editing
J.H.: data curation, writing – review & editing
N.S.: data curation, writing – review & editing
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A.C.: conceptualization, data curation, writing – original draft, and writing – review & editing

DECLARATION OF INTERESTS

The authors declared no conflicts of interest.

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