Insights into familial adult myoclonus epilepsy pathogenesis: how the same repeat expansion in six unrelated genes may lead to cortical excitability

Depienne, C.; Maagdenberg, A.M.J.M. van den; Kuhnel, T.; Ishiura, H.; Corbett, M.A.; Tsuji, S.

Received: 6 December 2022 | Revised: 22 December 2022 | Accepted: 6 January 2023

DOI: 10.1111/epi.17504

Epilepsia®

SPECIAL ISSUE ARTICLE

Insights into familial adult myoclonus epilepsy pathogenesis: How the same repeat expansion in six unrelated genes may lead to cortical excitability

Christel Depienne[1] | **Arn M. J. M. van den Maagdenberg**[2,3] | **Theresa Kühnel**[1] | **Hiroyuki Ishiura**[4,5] | **Mark A. Corbett**[6] | **Shoji Tsuji**[4,7]

[1]Institute of Human Genetics, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[2]Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands

[3]Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

[4]Department of Neurology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

[5]Department of Neurology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[6]Robinson Research Institute, University of Adelaide, Adelaide Medical School, Adelaide, South Australia, Australia

[7]Institute of Medical Genomics, International University of Health and Welfare, Chiba, Japan

Correspondence
Christel Depienne, Institute of Human Genetics, University Hospital Essen, University of Duisburg-Essen, Hufelandstraße 55, Essen 45122, Germany.
Email: christel.depienne@uk-essen.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: Project number 455314768

Abstract

Familial adult myoclonus epilepsy (FAME) results from the same pathogenic TTTTA/TTTCA pentanucleotide repeat expansion in six distinct genes encoding proteins with different subcellular localizations and very different functions, which poses the issue of what causes the neurobiological disturbances that lead to the clinical phenotype. Postmortem and electrophysiological studies have pointed to cortical hyperexcitability as well as dysfunction and neurodegeneration of both the cortex and cerebellum of FAME subjects. FAME expansions, contrary to the same expansion in *DAB1* causing spinocerebellar ataxia type 37, seem to have no or limited impact on their recipient gene expression, which suggests a pathophysiological mechanism independent of the gene and its function. Current hypotheses include toxicity of the RNA molecules carrying UUUCA repeats, or toxicity of polypeptides encoded by the repeats, a mechanism known as repeat-associated non-AUG translation. The analysis of postmortem brains of FAME1 expansion (in *SAMD12*) carriers has revealed the presence of RNA foci that could be formed by the aggregation of RNA molecules with abnormal UUUCA repeats, but evidence is still lacking for other FAME subtypes. Even when the expansion is located in a gene ubiquitously expressed, expression of repeats remains undetectable in peripheral tissues (blood, skin). Therefore, the development of appropriate cellular models (induced pluripotent stem cell-derived neurons) or the study of affected tissues in patients is required to elucidate how FAME repeat expansions located in unrelated genes lead to disease.

KEYWORDS

cortical excitability, familial adult myoclonus epilepsy, RAN translation, repeat expansion, RNA toxicity

1 | INTRODUCTION: CHARACTERISTICS OF PATHOGENIC PENTANUCLEOTIDE REPEAT EXPANSIONS CAUSING FAMILIAL ADULT MYOCLONUS EPILEPSY

Familial adult myoclonus epilepsy (FAME) is a rare autosomal dominant disorder characterized by the association of cortical tremor, cortical myoclonus, and epileptic seizures, either comanifesting in a single individual or occurring in different combinations in members of the same family. This clinically variable but well-defined condition has been described using different acronyms such as benign adult familial myoclonic epilepsy (BAFME),[1] autosomal dominant cortical myoclonus and epilepsy (ADCME),[2] or familial cortical myoclonic tremor with epilepsy (FCMTE).[3] Early genetic investigations demonstrated locus heterogeneity with possible genetic causes mapped on different chromosomes.[4] Recent evidence, however, has revealed that the underlying pathogenic variants correspond to the same pentanucleotide repeat expansion in introns of six different genes: *SAMD12* on chromosome 8q24.1 (FAME1/BAFME),[5] *STARD7* on chromosome 2q11.2 (FAME2/ADCME/BAFME),[6] *MARCHF6* on chromosome 5p15.2 (FAME3/FCMTE),[7] *YEATS2* on chromosome 3q27.1 (FAME4),[8] *TNRC6A* on chromosome 16q12.1 (FAME6/BAFME6),[5] and *RAPGEF2* on chromosome 4q32.1 (FAME7/BAFME7).[5] In all six genes, FAME expansions occur at a polymorphic short tandem repeat originally composed of TTTTA repeats, usually adjacent to one or more Alu repeats. Contrary to nonpathogenic repeats, pathogenic expansions are invariably composed of two different motifs: a TTTTA repeat stretch, which is expanded compared to the reference sequence, associated with TTTCA repeats that are never observed at any FAME locus in healthy populations and therefore considered genomic insertions. The size of pathogenic repeat expansions varies between 2.2 and 18.4 kb on average (i.e., 440 and 3600 repeats) including both motifs.[5–7] Furthermore, these expansions are unstable in a length-dependent manner with the largest expansions manifesting the highest degree of somatic variability.[7]

2 | INSIGHTS FROM ELECT ROPHYSIOLOGICAL AND POSTMORTEM STUDIES

Electrophysiological investigations, including electroencephalography, electromyography, and somatosensory evoked potentials, have convincingly shown that cortical myoclonus results from abnormal electrical discharges in the cerebral cortex. FAME clinical manifestations seem to represent a continuum encompassing spontaneous cortical tremor/myoclonus, cortical reflex myoclonus (i.e., cortical myoclonus provoked by sensory stimuli), and generalized epilepsy, the latter being characterized by a more widespread abnormal cortical activity than cortical myoclonus alone.[3,9,10] This overall suggests that FAME is the result of cortical hyperexcitability. However, the pathophysiological mechanisms at play could also involve dysfunction and/or progressive neurodegeneration of other brain structures, particularly the cerebellum, as well as alterations of cerebellothalamocortical circuits.[11] Morphologic changes and mild and diffuse loss of Purkinje cells in postmortem brain studies of FAME patients have been observed. Moreover, halolike amorphous materials immunopositive for calbindin were observed in the cytoplasm of Purkinje cells of a subject with a homozygous repeat expansion in *SAMD12*,[5] a finding reminiscent of inclusions observed in other repeat expansion disorders.[12,13] Nevertheless, it is not clear whether these relatively mild morphological changes occur at an early or late stage of disease progression and, therefore, correspond to primary or secondary processes in FAME pathogenesis.

Key Points

- Repeat expansions in six genes encoding proteins involved in different pathways cause FAME
- FAME pathogenesis appears to be independent of the gene where the repeats are located or its function
- FAME likely results from cortical hyperexcitability and dysfunction or neurodegeneration of the cortex and cerebellum
- Possible pathomechanisms include toxicity of UUUCA repeats at the RNA level and repeat-associated non-AUG translation

3 | GENES IN WHICH FAME REPEAT EXPANSIONS OCCUR ARE UNRELATED

The six genes harboring FAME-associated repeat expansions encode proteins with very different subcellular localizations and functions. *SAMD12* (sterile alpha motif domain-containing 12) encodes a small protein (22 kDa) of unknown function localized at the cytoplasmic side of the plasma membrane (source: UniProt). *STARD7* (StAR-related lipid transfer domain-containing 7) encodes a

mitochondrial protein involved in lipid transport and metabolism.[14] *MARCHF6* (membrane-associated ring-CH-type finger 6) encodes an E3 ubiquitin ligase that mediates the degradation of misfolded or damaged proteins in the endoplasmic reticulum.[15,16] *YEATS2* (YEATS domain-containing 2) codes for a subunit of the nuclear ADA2A-containing histone acetyltransferase complex.[17] *RAPGEF2* (Rap guanine nucleotide exchange factor 2) encodes a guanine nucleotide exchange factor transiting between the cytoplasm, endosomes, and the plasma membrane, and regulating the Ras-Raf-MEK-ERK signal transduction pathway.[18,19] Finally, *TNRC6A* (trinucleotide repeat-containing gene 6A protein, also called glycine/tryptophane repeat protein GW182) encodes a component of a cytoplasmic ribonucleoprotein complex involved in regulating mRNA silencing, stability, and translation.[20] The expression profiles of these six genes are also different; some are predominantly expressed in the central nervous system (including neurons, e.g., *RAPGEF2*), whereas others are ubiquitously expressed.[21] Genes with FAME repeat expansions therefore have no obvious common characteristics and belong to different biological pathways.

Contrary to other repeat expansion disorders, such as fragile X syndrome or Friedreich ataxia, where expansions lead to an epigenetic loss of function of the corresponding gene, current evidence suggests that FAME expansions do not significantly alter expression, splicing, and overall function of the gene in which they reside. Therefore, the most logical scenario implies that the underlying pathological mechanisms are independent of the gene itself or its function. This hypothesis is further supported by an absence of change in expression or splicing of *STARD7* and *MARCHF6* in blood cells and fibroblasts of FAME2 and FAME3 patients, where these genes are relatively highly expressed.[6,7] However, the real impact of repeat expansions on gene expression in affected tissues deserves further study, as it may also reveal subtle differences between FAME subtypes. The study of *SAMD12* expression in postmortem brains of FAME1 expansion carriers, for instance, suggests that transcription may terminate at the site of the expansion. This finding was associated with a slight but significant reduction of SAMD12 protein expression.[5]

4 | STRUCTURES OF REPEAT EXPANSIONS POINT TO PATHOGENICITY OF TTTCA REPEATS

Various observations suggest that TTTCA and not TTTTA repeats constitute the pathogenic part of the expansion. First, expanded TTTTA repeats (>500 bp) in *SAMD12* are present in 6% of healthy subjects in the Japanese population, indicating that pure TTTTA expansions are nonpathogenic.[5,22] Second, there is an inverse correlation existing between the age at onset and the length of FAME3 expansions, mainly driven by the size of TTTCA repeats.[7] TTTCA repeats are usually located at the 3′ end of the expansion, that is, 5′-$(TTTTA)_{exp}(TTTCA)_{exp}$-3′, but TTTCA repeats have also been, although rarely, described in between two expanded TTTTA expanded stretches (5′-$[TTTTA]_{exp}[TTTCA]_{exp}[TTTTA]_{exp}$-3′).

The existence of pathogenic motifs other than TTTCA was suggested by the identification of a 5′-$(TTTTA)_{exp}(TTTGA)_{exp}$-3 expansion segregating with FAME in a large Chinese pedigree.[23] However, other findings have shown that pathogenic expansions may contain not one but two or more inserted motifs (e.g., TTTCA and TTTGA repeats),[24] and because of the high degree of somatic mosaicism, it may be difficult to have a full overview of all possible repeat structures existing in cells of one individual, especially because genetic analyses currently performed usually assess only a few alleles, or include biases linked to amplification or selection of alleles that can effectively be sequenced. The pathogenicity threshold for the number of TTTCA repeats remains unclear, but the smallest number of TTTCA repeats contained within larger TTTTA expansions described in FAME patients so far is 14.[24]

5 | REPEAT EXPRESSION, RNA TOXICITY, AND RNA FOCI

Although pathogenic expansions seem independent of the gene they are located in, they are consistently located in introns of genes expressed in FAME-affected brain structures (i.e., cortex and cerebellum) and not in intergenic regions (Figure 1A). This suggests that the location of repeats in transcriptionally active regions of the genome is required for pathogenesis. Transcription of RNA molecules encompassing the repeats is likely a key event in the disease process, and the genes may hence serve as a vehicle for repeat expression.

Nevertheless, conflicting data exist regarding the transcription of RNA-containing repeats. On the one hand, reads filled with UUUUA/UUUCA repeats were detected in the liver, lymphoblastic cells, and postmortem brains of FAME1 patients. RNA foci were also detected in cortical neurons and Purkinje cells of the same brains by RNA fluorescence in situ hybridization using a Cy3-$(TGAAA)_{12}$ probe targeting UUUCA repeats.[5] On the other hand, no reads filled with UUUUA/UUUCA repeats were detectable in blood and fibroblasts of FAME2 and FAME3 patients,[6,7] although *STARD7* and *MARCHF6* are highly expressed in these tissues. This may suggest that

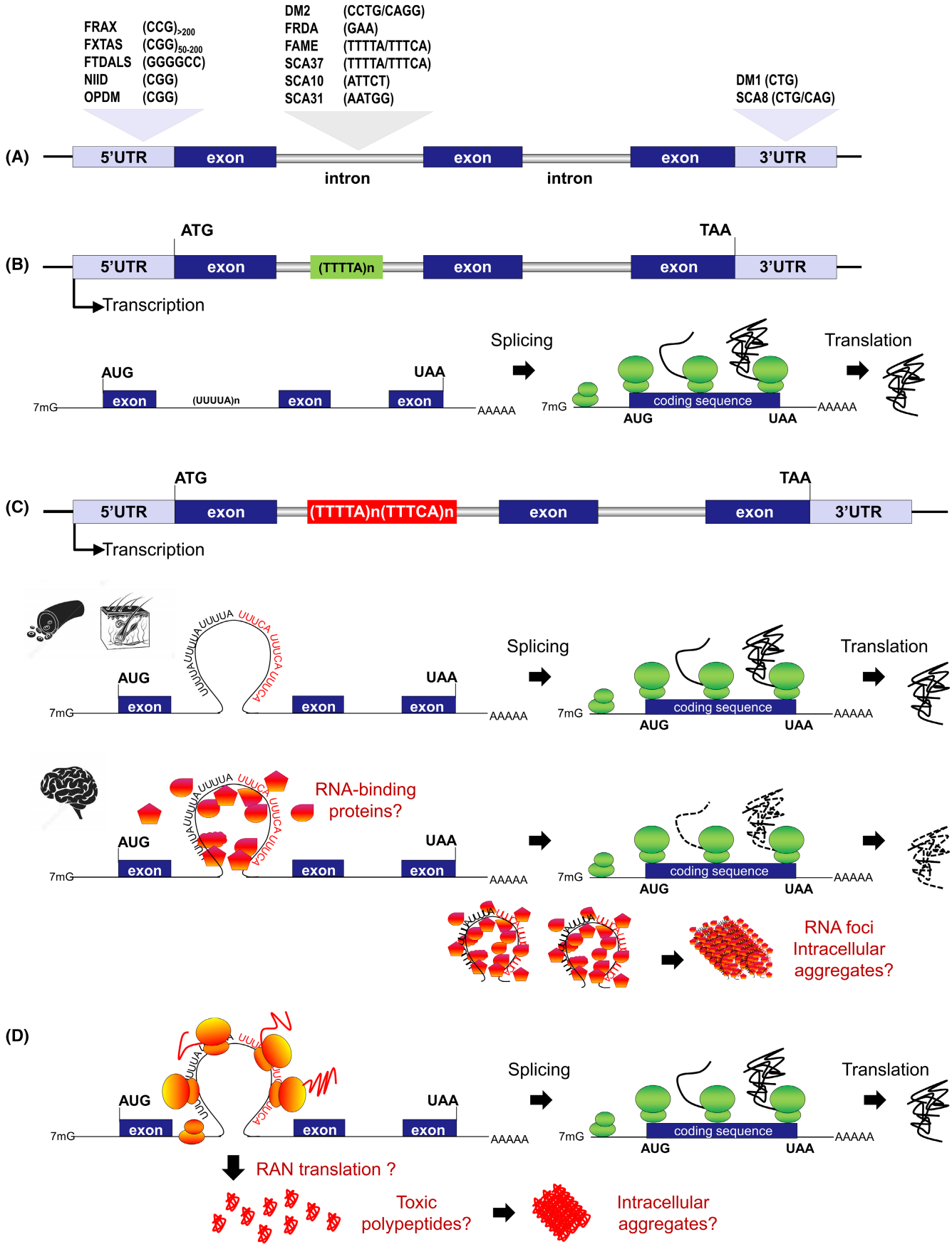

FIGURE 1 Possible mechanisms associated with TTTCA repeat expansions in familial adult myoclonus epilepsy (FAME). (A) Summary of the repeat expansion disorders discussed in this review, featuring their location within genes and repeat motif (in parentheses). (B) Schematic representation of possible pathomechanisms associated with FAME, showing normal situation of a gene with nonpathogenic intronic TTTTA repeats. Transcription, splicing, and translation occur normally in tissues where the gene is expressed. (C) Abnormal situation with pathogenic association of TTTTA and TTTCA repeats and a possible gain of function at the RNA level. Upper graph: In peripheral tissues (blood, skin), UUUCA repeats do not alter gene expression, splicing, or translation. Lower graph: In the brain, UUUCA repeats may bind neuron-specific RNA-binding proteins and form RNA foci and intracellular aggregates. This mechanism, described in myotonic dystrophy type 1 (DM1) and DM2, is supported by data obtained from postmortem brains with FAME1 (*SAMD12*) repeat expansions. (D) Abnormal situation with pathogenic association of TTTTA and TTTCA repeats and a possible gain of function at the protein level. UUUUA/UUUCA repeats may get translated through repeat-associated non-ATG (RAN) translation and form polypeptides that are toxic and/or able to form intracellular aggregates. This mechanism has been shown for several repeat expansion disorders (including fragile X-associated tremor and ataxia syndrome [FXTAS], neuronal intranuclear inclusion disease [NIID], oculopharyngodistal myopathy [OPDM], DM1, DM2, spinocerebellar ataxia type 8 [SCA8], and SCA31, but not SCA10) but has not yet been demonstrated in FAME. FRAX, fragile X syndrome; FRDA, Friedreich ataxia; FTDALS, frontotemporal dementia/amyotrophic lateral sclerosis; UTR, untranslated region; 7mG, 7-methylguanosine cap of mRNA

persistence or accumulation of RNA molecules containing UUUCA repeats is brain-specific and does not occur in peripheral tissues.

Observations from FAME1 postmortem brains strongly suggest that transcribed RNA molecules with pathological repeats can accumulate, aggregate, and form RNA foci. This process is reminiscent of the mechanism described in myotonic dystrophy type 1 (DM1) and DM2, respectively caused by CTG repeat expansions in the 3'-untranslated region of *DMPK*[25] and intronic CCTG repeat expansions in *CNBP*.[26] RNA molecules with these repeats adopt stable secondary structures (e.g., hairpins) recognized by specific RNA-binding proteins, including muscle-blind-like (MBNL1) proteins. These proteins are sequestered in nuclear aggregates formed by RNA foci, which subsequently leads to their loss of function and accumulation of tissue-specific splicing defects.[27–30] In this context, it is possible that FAME could also result from the abnormal accumulation of RNA molecules recruiting UUUCA-binding proteins expressed in a neuron-specific manner (Figure 1C). If true, an abnormal expression or splicing of genes targeted by these RNA-binding proteins should also be observed. The RNA toxicity hypothesis is further supported by the observation of RNA foci forming when UUUCA repeats are overexpressed in HEK293T cells and both developmental defects and increased lethality as a result of the overexpression of UUUCA but not UUUUA repeats in zebrafish.[31] Nonetheless, the existence of RNA with UUUCA repeats and RNA foci needs further confirmation in other FAME subtypes.

6 | REPEAT-ASSOCIATED NON-AUG TRANSLATION

Another possible pathogenic mechanism associated with FAME repeat expansions is repeat-associated non-AUG (RAN) translation.[32] Originally described in spinocerebellar ataxia (SCA) type 8 and DM1, RAN translation is a noncanonical translation process that occurs at repeat expansion sites in the absence of an AUG start codon.[33] In theory, translation of polypeptides directly from pathological repeats is possible in all reading frames on both sense and antisense DNA strands.[33,34] However, recent studies suggest that in some expansion disorders, translation occurs only when the expansion creates a novel open reading frame initiated by an AUG or another possible (near-cognate) initiation codon located upstream of the repeats, thus leading to the expression of one main polypeptide from a single frame.[35] The produced polypeptides may be toxic or prone to aggregation, as previously described for proteins with polyglutamine expansions.[34] The list of repeat expansion disorders in which peptides are translated from the expanded repeats is increasing and includes DM2, SCA31, fragile X-associated tremor and ataxia syndrome, neuronal intranuclear inclusion disease, *C9ORF72*-related frontotemporal dementia/amyotrophic lateral sclerosis, and also possibly oculopharyngodistal myopathy.[12,34–36] So far, there is no evidence that RAN translation occurs in FAME. Only two polypeptides, respectively translated from TTTTA (polyFYFIL) and TTTCA (polyFHFIS), could theoretically be produced, and reading frames on the reverse strand lead to early termination codons (Figure 1D). Furthermore, toxicity at the RNA and protein level are mutually nonexclusive and could even be intimately linked during disease progression.[37,38]

7 | INSIGHTS FROM OTHER NONCODING PENTANUCLEOTIDE EXPANSIONS

A puzzling observation is that TTTTA/TTTCA expansions, before being identified as the main cause of FAME, had already been described as the cause of SCA type 37 (SCA37).

SCA37 is due to TTTTA/TTTCA repeat expansion in *DAB1*, a gene on chromosome 1p32.2 encoding a downstream effector of the reelin signaling pathway.[31] SCA37 is an adult onset, progressive neurodegenerative condition characterized by gait and limb ataxia, dysmetria, dysarthria, and nystagmus. So far, none of the individuals with this disorder has been reported to have cortical tremor, myoclonus, or epilepsy.[31] This challenges all hypotheses about possible mechanisms that could be involved in FAME. Given the high expression of *DAB1* in cortex and cerebellum, TTTTA/TTTCA repeats should also be transcribed as part of *DAB1* pre-mRNA in these brain regions. Logically, mechanisms implying toxicity at the RNA and/or protein level should also apply and lead to a similar disease. One major difference, however, could reside in the impact of the repeat expansion on *DAB1* expression; contrary to FAME repeat expansions, SCA37 expansions result in increased expression of *DAB1* and inclusion of two exons normally absent from the isoforms expressed in the cerebellum in postmortem brains of affected individuals.[39] In addition, SCA37 TTTCA repeats tend to be shorter in size (1–3 kb) and have a different structure compared to those in FAME expansions, with the TTTCA stretch being located in between TTTTA repeats. However, as in FAME, nonpathogenic expansions (up to 3 kb) composed of TTTTA repeats also exist at the *DAB1* locus, further confirming that homogeneous TTTTA expansions are benign independently of the gene. In conclusion, it is likely that FAME repeat expansions lead to disease independently of the gene where the repeats are expanded, contrary to SCA37, in which expression of *DAB1*, a gene with a known function in cerebellar and cortex development, would be altered. However, there are many uncertainties remaining, in particular why the expression of UUUCA repeats does not lead to cortical hyperexcitability in SCA37.

Two other SCAs types are also caused by pentanucleotide repeats: SCA10, associated with an ATTCT repeat expansion in *ATXN10*,[40] and SCA31, associated with an AATGG expansions in *BEAN1*.[41] SCA10 expansions are mainly found in Latin American countries (with a probable founder effect originating from the Indigenous American population) and are associated with a clinically variable phenotype, either presenting as a pure cerebellar ataxia or as a combination of ataxia and seizures.[42] Interruptions, that is, the presence of alternative motifs such as ATTGT, ATCCT, or ATTCC within the expansions, have been associated with an increased risk of epilepsy.[43] Recent evidence even suggests that only interrupted expansions are pathogenic, whereas pure expansions composed of ATTCT repeats are either nonpathogenic or associated with late onset Parkinsonism, a finding reminiscent of pathological repeat configurations observed in FAME.[44] RNA foci containing the AUUCU repeat have been described in fibroblasts of SCA10 patients and in an SCA10 mouse model. This model, in which AUUCU repeats are specifically overexpressed in the context of a LacZ transgene, has revealed that aggregating AUUCU repeats specifically recruit hnRNP K, leading to loss of its function through a mechanism similar to that described for myotonic dystrophy type 1.[45,46] However, the transgenic model and suggested mechanism do not fully recapitulate the human pathology and explain why only interrupted repeats would be pathogenic.

8 | PERSPECTIVES: WHICH MODEL(S) SHOULD BE USED TO STUDY FAME PATHOGENIC MECHANISMS?

The examples discussed above highlight the necessity but also the complexity of studying repeat expansions in their native gene context. The tandem repeats at the origin of pathological expansions are primate- or human-specific, and the size and high A/T content of FAME expansions make their amplification and cloning difficult, thus limiting possibilities to develop animal models. Animal models, including mouse, drosophila,[47] and zebrafish[31] have been used with success in other repeat disorders, but they are usually based on massive overexpression of repeats, a condition that might not faithfully represent what happens in patients' tissues. Disease mechanisms may not be observable in peripheral tissues (blood cells, fibroblasts) and require modeling directly in postmitotic noncycling neuronal cells. The reprogramming of patients' cells into induced pluripotent stem cells that can be differentiated into neurons or inducing neurons directly from fibroblasts[48] may thus represent the best approach to model relevant disease processes. However, recapitulating the human pathology in any cellular or animal model might take decades, a condition almost impossible to achieve. One possible way to overcome this obstacle may be to accelerate the disease process by focusing on very large repeat expansions or artificially increasing neuron-specific repeat expression, but the validity of observed mechanisms would need independent confirmation in postmortem human brain samples. Understanding how FAME expansions lead to disease at the molecular and cellular level will be an important step toward the development of personalized medicine aimed at reversing or delaying progression of the disease.

AUTHOR CONTRIBUTIONS

Christel Depienne drafted the manuscript. Arn M. J. M. van den Maagdenberg, Theresa Kühnel, Hiroyuki Ishiura,

Mark A. Corbett, and Shoji Tsuji revised the manuscript for intellectual content. All authors approved the final manuscript.

ACKNOWLEDGMENTS

This communication was part of the International Workshop on Familial Adult Myoclonic Epilepsy, held in Naples (Italy) on May 27–28, 2022. This Networking event has received funding from the European Union's Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575. The authors would like to thank more particularly Pasquale Striano and Antonietta Coppola who conceived and coordinated the series of reviews on familial adult myoclonus epilepsy. Open Access funding was enabled and supported by Projekt DEAL.

FUNDING INFORMATION

The study on FAME in Germany is supported by a Deutsche Forschungsgemeinschaft grant (project number 455314768 to C.D.).

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ORCID

Christel Depienne https://orcid.org/0000-0002-7212-9554
Arn M. J. M. van den Maagdenberg https://orcid.org/0000-0002-9310-5535
Theresa Kühnel https://orcid.org/0000-0003-0629-3521
Hiroyuki Ishiura https://orcid.org/0000-0003-2975-7309
Mark A. Corbett https://orcid.org/0000-0001-9298-3072
Shoji Tsuji https://orcid.org/0000-0001-5602-5686

REFERENCES

1. Kuwano A, Takakubo F, Morimoto Y, Uyama E, Uchino M, Ando M, et al. Benign adult familial myoclonus epilepsy (BAFME): an autosomal dominant form not linked to the dentatorubral pallidoluysian atrophy (DRPLA) gene. J Med Genet. 1996 Jan;33:80–1.
2. Guerrini R, Bonanni P, Patrignani A, Brown P, Parmeggiani L, Grosse P, et al. Autosomal dominant cortical myoclonus and epilepsy (ADCME) with complex partial and generalized seizures: a newly recognized epilepsy syndrome with linkage to chromosome 2p11.1-q12.2. Brain. 2001 Dec;124:2459–75.
3. van Rootselaar AF, van Schaik IN, van den Maagdenberg AM, Koelman JH, Callenbach PM, Tijssen MAJ. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. Mov Disord. 2005 Jun;20:665–73.
4. van den Ende T, Sharifi S, van der Salm SMA, van Rootselaar AF. Familial cortical myoclonic tremor and epilepsy, an enigmatic disorder: from phenotypes to pathophysiology and genetics. A systematic review. Tremor Other Hyperkinet Mov (N Y). 2018;8:503.
5. Ishiura H, Doi K, Mitsui J, Yoshimura J, Matsukawa MK, Fujiyama A, et al. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. Nat Genet. 2018 Apr;50:581–90.
6. Corbett MA, Kroes T, Veneziano L, Bennett MF, Florian R, Schneider AL, et al. Intronic ATTTC repeat expansions in STARD7 in familial adult myoclonic epilepsy linked to chromosome 2. Nat Commun. 2019 Oct 29;10:4920.
7. Florian RT, Kraft F, Leitao E, Kaya S, Klebe S, Magnin E, et al. Unstable TTTTA/TTTCA expansions in MARCH6 are associated with Familial Adult Myoclonic Epilepsy type 3. Nat Commun. 2019 Oct 29;10:4919.
8. Yeetong P, Pongpanich M, Srichomthong C, Assawapitaksakul A, Shotelersuk V, Tantirukdham N, et al. TTTCA repeat insertions in an intron of YEATS2 in benign adult familial myoclonic epilepsy type 4. Brain. 2019 Nov 1;142:3360–6.
9. Lagorio I, Zara F, Striano S, Striano P. Familial adult myoclonic epilepsy: a new expansion repeats disorder. Seizure. 2019 Apr;67:73–7.
10. Latorre A, Rocchi L, Magrinelli F, Mulroy E, Berardelli A, Rothwell JC, et al. Unravelling the enigma of cortical tremor and other forms of cortical myoclonus. Brain. 2020 Sep 1;143:2653–63.
11. van Rootselaar AF, van den Maagdenberg A, Depienne C, Tijssen MAJ. Pentameric repeat expansions: cortical myoclonus or cortical tremor? Brain. 2020 Oct 1;143:e86.
12. Ishiura H, Tsuji S. Advances in repeat expansion diseases and a new concept of repeat motif-phenotype correlation. Curr Opin Genet Dev. 2020 Dec;65:176–85.
13. Depienne C, Mandel JL. 30 years of repeat expansion disorders: what have we learned and what are the remaining challenges? Am J Hum Genet. 2021 Mar 29;108(5):764–85.
14. Flores-Martin J, Rena V, Angeletti S, Panzetta-Dutari GM, Genti-Raimondi S. The Lipid Transfer Protein StarD7: structure, function, and regulation. Int J Mol Sci. 2013 Mar 18;14:6170–86.
15. Zattas D, Berk JM, Kreft SG, Hochstrasser M. A conserved C-terminal element in the yeast Doa10 and human MARCH6 ubiquitin ligases required for selective substrate degradation. J Biol Chem. 2016 Jun 3;291:12105–18.
16. Stefanovic-Barrett S, Dickson AS, Burr SP, Williamson JC, Lobb IT, van den Boomen DJ, et al. MARCH6 and TRC8 facilitate the quality control of cytosolic and tail-anchored proteins. EMBO Rep. 2018 May;19:e45603.
17. Wang YL, Faiola F, Xu M, Pan S, Martinez E. Human ATAC Is a GCN5/PCAF-containing acetylase complex with a novel NC2-like histone fold module that interacts with the TATA-binding protein. J Biol Chem. 2008 Dec 5;283:33808–15.
18. Jiang SZ, Xu W, Emery AC, Gerfen CR, Eiden MV, Eiden LE. NCS-Rapgef2, the protein product of the neuronal Rapgef2 gene, is a specific activator of D1 dopamine receptor-dependent ERK phosphorylation in mouse brain. eNeuro. 2017 Sep–Oct;4:ENEURO.0248-17.2017.
19. Emery AC, Eiden MV, Mustafa T, Eiden LE. Rapgef2 connects GPCR-mediated cAMP signals to ERK activation in neuronal and endocrine cells. Sci Signal. 2013 Jun 25;6:ra51.
20. Nishi K, Nishi A, Nagasawa T, Ui-Tei K. Human TNRC6A is an Argonaute-navigator protein for microRNA-mediated gene silencing in the nucleus. RNA. 2013 Jan;19:17–35.
21. onsortium GT, Laboratory DA, Coordinating Center -Analysis Working G, Statistical Methods groups-Analysis

Working G, Enhancing Gg, Fund NIHC et al. Genetic effects on gene expression across human tissues. Nature. 2017 Oct 11;550:204–13.
22. Pan S, Li X, Li L, Lin H, Wang D, Zhang X, et al. Comprehensive genetic, clinical and electrophysiological studies of familial cortical myoclonic tremor with epilepsy 1 highlight the role of gene configurations. Seizure. 2021 Apr;87:69–74.
23. Cen Z, Chen Y, Yang D, Zhu Q, Chen S, Chen X, et al. Intronic (TTTGA)n insertion in SAMD12 also causes familial cortical myoclonic tremor with epilepsy. Mov Disord. 2019 Oct;34:1571–6.
24. Mizuguchi T, Toyota T, Miyatake S, Mitsuhashi S, Doi H, Kudo Y, et al. Complete sequencing of expanded SAMD12 repeats by long-read sequencing and Cas9-mediated enrichment. Brain. 2021 May 7;144:1103–17.
25. Mahadevan M, Tsilfidis C, Sabourin L, Shutler G, Amemiya C, Jansen G, et al. Myotonic dystrophy mutation: an unstable CTG repeat in the 3′ untranslated region of the gene. Science. 1992 Mar 6;255:1253–5.
26. Liquori CL, Ricker K, Moseley ML, Jacobsen JF, Kress W, Naylor SL, et al. Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9. Science. 2001 Aug 3;293:864–7.
27. Botta A, Rinaldi F, Catalli C, Vergani L, Bonifazi E, Romeo V, et al. The CTG repeat expansion size correlates with the splicing defects observed in muscles from myotonic dystrophy type 1 patients. J Med Genet. 2008 Oct;45:639–46.
28. Ashizawa T, Sarkar PS. Myotonic dystrophy types 1 and 2. Handb Clin Neurol. 2011;101:193–237.
29. Lucchiari S, Pagliarani S, Corti S, Mancinelli E, Servida M, Fruguglietti E, et al. Colocalization of ribonuclear inclusions with muscle blind like-proteins in a family with myotonic dystrophy type 2 associated with a short CCTG expansion. J Neurol Sci. 2008 Dec 15;275:159–63.
30. Jiang H, Mankodi A, Swanson MS, Moxley RT, Thornton CA. Myotonic dystrophy type 1 is associated with nuclear foci of mutant RNA, sequestration of muscleblind proteins and deregulated alternative splicing in neurons. Hum Mol Genet. 2004 Dec 15;13:3079–88.
31. Seixas AI, Loureiro JR, Costa C, Ordonez-Ugalde A, Marcelino H, Oliveira CL, et al. A pentanucleotide ATTTC repeat insertion in the non-coding region of DAB1, mapping to SCA37, Causes Spinocerebellar Ataxia. Am J Hum Genet. 2017 Jul 6;101:87–103.
32. Banez-Coronel M, Ranum LPW. Repeat-associated non-AUG (RAN) translation: insights from pathology. Lab Invest. 2019 Jul;99:929–42.
33. Zu T, Gibbens B, Doty NS, Gomes-Pereira M, Huguet A, Stone MD, et al. Non-ATG-initiated translation directed by microsatellite expansions. Proc Natl Acad Sci U S A. 2011 Jan 4;108:260–5.
34. Glineburg MR, Todd PK, Charlet-Berguerand N, Sellier C. Repeat-associated non-AUG (RAN) translation and other molecular mechanisms in Fragile X Tremor Ataxia Syndrome. Brain Res. 2018 Aug 15;1693:43–54.
35. Boivin M, Deng J, Pfister V, Grandgirard E, Oulad-Abdelghani M, Morlet B, et al. Translation of GGC repeat expansions into a toxic polyglycine protein in NIID defines a novel class of human genetic disorders: the polyG diseases. Neuron. 2021 Jun 2;109:1825–35.e5.
36. Malik I, Kelley CP, Wang ET, Todd PK. Molecular mechanisms underlying nucleotide repeat expansion disorders. Nat Rev Mol Cell Biol. 2021 Sep;22:589–607.
37. Schwartz JL, Jones KL, Yeo GW. Repeat RNA expansion disorders of the nervous system: post-transcriptional mechanisms and therapeutic strategies. Crit Rev Biochem Mol Biol. 2021 Feb;56:31–53.
38. Swinnen B, Robberecht W, Van Den Bosch L. RNA toxicity in non-coding repeat expansion disorders. EMBO J. 2020 Jan 2;39:e101112.
39. Corral-Juan M, Serrano-Munuera C, Rabano A, Cota-Gonzalez D, Segarra-Roca A, Ispierto L, et al. Clinical, genetic and neuropathological characterization of spinocerebellar ataxia type 37. Brain. 2018 Jul 1;141:1981–97.
40. Matsuura T, Yamagata T, Burgess DL, Rasmussen A, Grewal RP, Watase K, et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat Genet. 2000 Oct;26:191–4.
41. Sato N, Amino T, Kobayashi K, Asakawa S, Ishiguro T, Tsunemi T, et al. Spinocerebellar ataxia type 31 is associated with "inserted" penta-nucleotide repeats containing (TGGAA)n. Am J Hum Genet. 2009 Nov;85:544–57.
42. Kurosaki T, Ashizawa T. The genetic and molecular features of the intronic pentanucleotide repeat expansion in spinocerebellar ataxia type 10. Front Genet. 2022;13:936869.
43. McFarland KN, Liu J, Landrian I, Zeng D, Raskin S, Moscovich M, et al. Repeat interruptions in spinocerebellar ataxia type 10 expansions are strongly associated with epileptic seizures. Neurogenetics. 2014 Mar;15:59–64.
44. Morato Torres CA, Zafar F, Tsai YC, Vazquez JP, Gallagher MD, McLaughlin I, et al. ATTCT and ATTCC repeat expansions in the ATXN10 gene affect disease penetrance of spinocerebellar ataxia type 10. HGG Adv. 2022 Oct 13;3:100137.
45. White M, Xia G, Gao R, Wakamiya M, Sarkar PS, McFarland K, et al. Transgenic mice with SCA10 pentanucleotide repeats show motor phenotype and susceptibility to seizure: a toxic RNA gain-of-function model. J Neurosci Res. 2012 Mar;90:706–14.
46. White MC, Gao R, Xu W, Mandal SM, Lim JG, Hazra TK, et al. Inactivation of hnRNP K by expanded intronic AUUCU repeat induces apoptosis via translocation of PKCdelta to mitochondria in spinocerebellar ataxia 10. PLoS Genet. 2010 Jun 10;6:e1000984.
47. Shibata T, Nagano K, Ueyama M, Ninomiya K, Hirose T, Nagai Y, et al. Small molecule targeting r(UGGAA)(n) disrupts RNA foci and alleviates disease phenotype in Drosophila model. Nat Commun. 2021 Jan 11;12:236.
48. Wang P, Zhang HL, Li W, Sha H, Xu C, Yao L, et al. Generation of patient-specific induced neuronal cells using a direct reprogramming strategy. Stem Cells Dev. 2014 Jan 1;23(23):16.

How to cite this article: Depienne C, van den Maagdenberg AMJM, Kühnel T, Ishiura H, Corbett MA, Tsuji S. Insights into familial adult myoclonus epilepsy pathogenesis: How the same repeat expansion in six unrelated genes may lead to cortical excitability. Epilepsia. 2023;64:S31–S38. https://doi.org/10.1111/epi.17504