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Rootselaar, A.F. van; Maagdenberg, A.M.J.M. van den; Depienne, C.; Tijssen, M.A.J.

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LETTER TO THE EDITOR

Pentameric repeat expansions: cortical myoclonus or cortical tremor?

Anne-Fleur van Rootselaar,[1,2] Arn M. J. M. van den Maagdenberg,[3,4] Christel Depienne[5] and Marina A. J. Tijssen[6,7]

1 Department of Neurology and Clinical Neurophysiology, Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands
2 Center for Rare Movement Disorders, Amsterdam UMC, Amsterdam, The Netherlands
3 Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
4 Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
5 Institute of Human Genetics, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
6 Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
7 Expertise Center Movement Disorders Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands

Correspondence to: Professor Marina A. J. Tijssen
Department of Neurology, University Medical Center Groningen
University of Groningen, 9700, AB, Groningen, The Netherlands
E-mail: m.a.j.de.koning-tijssen@umcg.nl

With great interest we read the paper by Latorre *et al.* (2020) titled 'Unravelling the enigma of cortical tremor and other forms of cortical myoclonus', which provides an update on autosomal dominant familial cortical myoclonic tremor and epilepsy [FCMTE/ADCME/familial adult myoclonic epilepsy (FAME)]. FCMTE is a rare syndrome that deserves the attention not only because of its specific clinical and electrophysiological features but surely because of its pathophysiology and truly intriguing genetic underpinning. FCMTE has the potential to become a textbook example of how very similar pentameric repeat expansions in different genes can result in a single phenotype. It is fascinating that the expansion itself, and not so much the gene it affects, seems the primary determinant of disease in FCMTE (Ishiura *et al.*, 2018; Florian *et al.*, 2019). With the identification of the repeat expansion as the generic cause of disease in FCMTE, with one blow the long quest for different causal mutations in various disease loci ended. Over the years no less than 10 putative disease genes (*SLC30A8*, *DCAF13*, *NOV*, *UBR5*, *PLA2G6*, *ACMSD*, *ADRA2B*, *CTNND2*, *CTNT2*, *NOL3*) have been put forward as causal genes for FCMTE1, FCMTE2, FCMTE3 and FCMTE5, for example, and the genetics and pathophysiology of most of them was reviewed in van de Ende *et al.* (2018), with the knowledge at the time, so before the first report of the identification of pentameric repeat expansions as the likely cause of disease in FCMTE (Ishiura *et al.*, 2018).

As our first comment, unfortunately, the paper by Latorre *et al.* did not include that FCMTE3/FAME3 on chromosome 5p15 is also associated with a pentameric repeat expansion (Florian *et al.*, 2019) and not a missense mutation in *CTNND2*, as we had suggested before (van Rootselaar *et al.*, 2017). Furthermore, it remains unclear whether *CNTN2* variants, reported in a single family so far, can cause FCMTE because of the absence of a replication study, a doubt about the phenotype and the impossibility to detect intronic repeat expansions using standard (whole exome) sequencing techniques used at the time (Stogmann *et al.*, 2013).

Our second comment refers to the central statement of Latorre *et al.* (2020) that 'despite pathophysiologically being a form of cortical myoclonus, cortical tremor is phenomenologically a tremor, likely driven by the cerebello-thalamo-cortical loop'. There is ongoing debate about the phenomenology of the distal tremulous movements in FCMTE. The movements themselves can indeed appear quite rhythmical and are easily mistaken for (essential) tremor (van de Ende *et al.*, 2018). However, on closer inspection, a jerky aspect and some irregularity can be appreciated, inconsistent with tremor (van Rootselaar *et al.*, 2005 and their Supporting Information). EMG analyses leave no doubt, showing short, irregular bursts and a frequency band rather than a frequency peak, in line with a high frequency

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continuous myoclonus, which argues against a tremor (van Rootselaar *et al.*, 2006). Based on these observations, 'cortical tremor' (FCTE) was renamed 'cortical myoclonic tremor' (FCMTE; van Rootselaar *et al.*, 2005). Notably, polyminimyoclonus, also a high-frequency action-induced distal movement disorder, sometimes with a quite rhythmical appearance, is classified as myoclonus.

As described by Latorre *et al.*, the pathophysiology of cortical myoclonic tremor, in fact myoclonus, and tremor differ. The electrophysiological hallmarks of FCMTE, including signs of cortical hyperexcitability and a cortical drive, are in line with epileptic myoclonus. In tremor, however, cortical excitability is normal and findings of EEG-EMG coupling around tremor frequency are not consistent (van Rootselaar *et al.*, 2006). Although both in tremor and in myoclonus, including FCMTE, involvement of the cerebello-thalamo-cortical loop—a part of the motor network—has been shown, the exact structures and nuclei involved in the involuntary movements likely differ. Deep brain stimulation (DBS) of the ventral intermediate (VIM) nucleus of the thalamus reduces tremor severity, whilst the target in drug resistant epilepsy is the anterior nucleus of the thalamus (ANT). Although FCMTE should be in the differential diagnosis of action tremor, it would be advisable to clearly distinguish FCMTE from tremor, because of the differences in pathophysiology, aetiology, in clinical approach, and because 'cortical tremor', in our opinion, is not a tremor phenomenologically. We would like to raise doubt with respect that truly rhythmical cortical tremor in FC(M)TE exists and propose to adhere to describing the movements in FCMTE as tremulous and classify these as myoclonus.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

References

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; 10: 4919.

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; 50: 581–90.

Latorre A, Rocchi L, Magrinelli F, Mulroy E, Berardelli A, Rothwel J, et al. Unravelling the enigma of cortical tremor and other forms of cortical myoclonus. Brain 2020. doi: 10.1093/brain/awaa129.

Stogmann E, Reinthaler E, Eltawil S, El Etribi MA, Hemeda M, El Nahhas N, et al. Autosomal recessive cortical myoclonic tremor and epilepsy: association with a mutation in the potassium channel associated gene CNTN2. Brain 2013; 136: 1155–60.

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. Tremor Other Hyperkinet Mov (New York, NY) 2018; 8: 503.

van Rootselaar AF, Groffen AJ, de Vries B, Callenbach PMC, Santen GWE, Koelewijn S, et al. δ-Catenin (CTNND2) missense mutation in familial cortical myoclonic tremor and epilepsy. Neurology 2017; 89: 2341–50.

van Rootselaar AF, Maurits NM, Koelman J, van der Hoeven JH, Bour LJ, Leenders KL, et al. Coherence analysis differentiates between cortical myoclonic tremor and essential tremor. Mov Disord 2006; 21: 215–22.

van Rootselaar AF, van Schaik IN, van den Maagdenberg AM, Koelman JH, Callenbach PM, Tijssen MA. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. Mov Disord 2005; 20: 665–73.