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COMMENTARY

Sleep-related hypermotor epilepsy—No longer controversial

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The evolution from nocturnal paroxysmal dystonia (NPD) to sleep-related hypermotor epilepsy (SHE) is a complex and fascinating journey, marked by numerous twists and discoveries.[1] This topic was recently reviewed by Fotedar and Luders,[2] who erroneously concluded that SHE is not an identifiable focal epilepsy syndrome as they believed that it is based on weak evidence. We wish to address errors in their analysis and offer a more balanced understanding of this important form of epilepsy.

1 | HISTORICAL RECONSTRUCTION

The authors[2]review more than 40 years of history largely through a lens based on electrophysiology and presurgical evaluation. They challenge the epileptic origin of SHE, previously termed nocturnal frontal lobe epilepsy (NFLE), now recognized as a well-characterized entity 3. Their chronological reconstruction, more comprehensively addressed in previous works,[1,4] seems arbitrary and incomplete, omitting key studies that have contributed significantly to the understanding of the epileptic origin of the syndrome. In particular, even before the debates on the true nature of NPD began, others had observed episodes similar to NPD in patients with confirmed epilepsy. From the 1970s, authorities in North America began to define frontal lobe epilepsy (nocturnal and diurnal), often misdiagnosed as psychiatric in origin (Figure 1).[3,5–18] The historical reconstruction presented in the review[2] is also incomplete in its identification of three eras marked by landmark studies (1972–1993, 1994–1998, 1999 to present), paying cursory attention to a crucial event: the Consensus Conference in Bologna,[17] which established diagnostic criteria for the syndrome (Table 1). The syndrome was subsequently accepted by the International League Against Epilepsy (ILAE) Commission on Terminology.[3] The consensus conference method is recommended for addressing important clinical questions in the face of limited high-quality evidence. The main outcome, a consensus statement, represents the collective opinions of an expert panel, derived from systematic review and discussion of available evidence.[19] The Bologna Consensus Conference was planned and completed between November 2013 and September 2014, using rigorous methods addressing conditions with limited evidence, such as rare diseases (see online appendix in Tinuper et al.[17] for details). The

final definition of the condition was reached through a transparent process that included predefined research questions, a systematic review for each question, an independent systematic mapping of the evidence,[20] an assessment of the literature's quality with reliable tools,[21,22] and an open, structured debate of 2 days involving a workgroup of experts for each the three main topics (clinical history; electro-clinical features; etiologic and pathogenic background) and a multidisciplinary international panel jury including specialists in child and adult epilepsy, sleep medicine, neurosurgery, genetics, epidemiology, and research methodology. The analysis explicitly covered all controversies and gray areas highlighted by Fotedar and Luders[2] (e.g., absence of a clear ictal rhythm does not exclude an epileptic origin, not all seizures in SHE are frontal in origin, and so on).

2 | TERMINOLOGY

Fotedar and Luders correctly delineate the change in terminology over decades but failed to note that terms such as paroxysmal arousal (PA),[23] epileptic nocturnal wandering (ENW),[24] and minor motor episodes or events (MMEs)[25,26] – have been long since abandoned.[3,17] We agree that not all episodes previously reported under the term "NPD" are unequivocally epileptic. However, there is robust evidence for an epileptic basis in many cases, based on consistent hypermotor seizure semiology observed in the same patient, both within the same night and over the years, supported by anatomo-electro-clinical data in some. The evolution of seizures with the same semiological onset but varying duration has led to seemingly distinct descriptors, ranging from very brief motor attacks (brief) to hypermotor seizures sometimes followed by prolonged complex ambulatory behavior (long). These have been subsequently recognized as part of the clinical spectrum of seizures in SHE, both within and between patients.[1]

3 | REFINEMENT OF SEMEIOLOGY OF SLEEP-RELATED PAROXYSMAL MOTOR EPISODES

Fotedar and Luders express frustration that influential neurologists in the mid-1990s led the community to believe that epilepsy was the basis for most sleep-related paroxysmal motor episodes.[14–16] They argued that all of these episodes were automatically assumed to be seizures and alternative diagnoses were often dismissed. This was never the case. Indeed, it is essential to recognize the extensive work that was done to clarify the differential diagnosis between sleep-related seizures and other sleep disorders (e.g., parasomnias), which remains a challenging but critical distinction. In that period, in addition to further electroclinical studies, diagnostic tools such as questionnaires and algorithms were developed, to aid clinicians in minimizing diagnostic errors in either direction, assessing the diagnostic accuracy of semiological patterns observed on video[27] or reported on clinical history.[28–33]

Key points

- The diagnostic category sleep-related hypermotor epilepsy (SHE) is recognized in the International League Against Epilepsy (ILAE) Classification as a syndrome with onset at any age. The diagnosis of SHE underwent a long process of evolution, reaching a pivotal milestone in 2016, when a multidisciplinary panel that was following recognized methodological standards formally defined its boundaries.
- Semiological terms, such as paroxysmal arousals, epileptic nocturnal wanderings, and minor motor episodes or events, have been abandoned as defining elements of SHE. The renaming of nocturnal frontal lobe epilepsy (NFLE) to SHE was necessary to acknowledge that many cases do not originate from the frontal lobe.
- Negative findings on electroencephalography (EEG; ictal and interictal) and magnetic resonance imaging (MRI) are common in many cases and do not preclude a diagnosis of SHE.
- Many research groups have confirmed autosomal dominant pathogenic variants in genes associated with SHE, including those encoding nicotinic receptor subunits and proteins of the mechanistic target of rapamycin (mTOR) pathway, highlighting the connection between genetic variants, clinical features, and ictal epileptiform changes.

4 | EEG AND MRI

Fotedar and Luders emphasize that the frequency of definitive interictal epileptiform changes on the electroencephalography (EEG) recordings of pre-surgical SHE cases is considerably higher than that seen in familial cases of SHE and even in a series of sporadic cases. We agree with this observation, which is likely an artifact of ascertainment bias, EEG recording time, and etiology. Pre-surgical cases

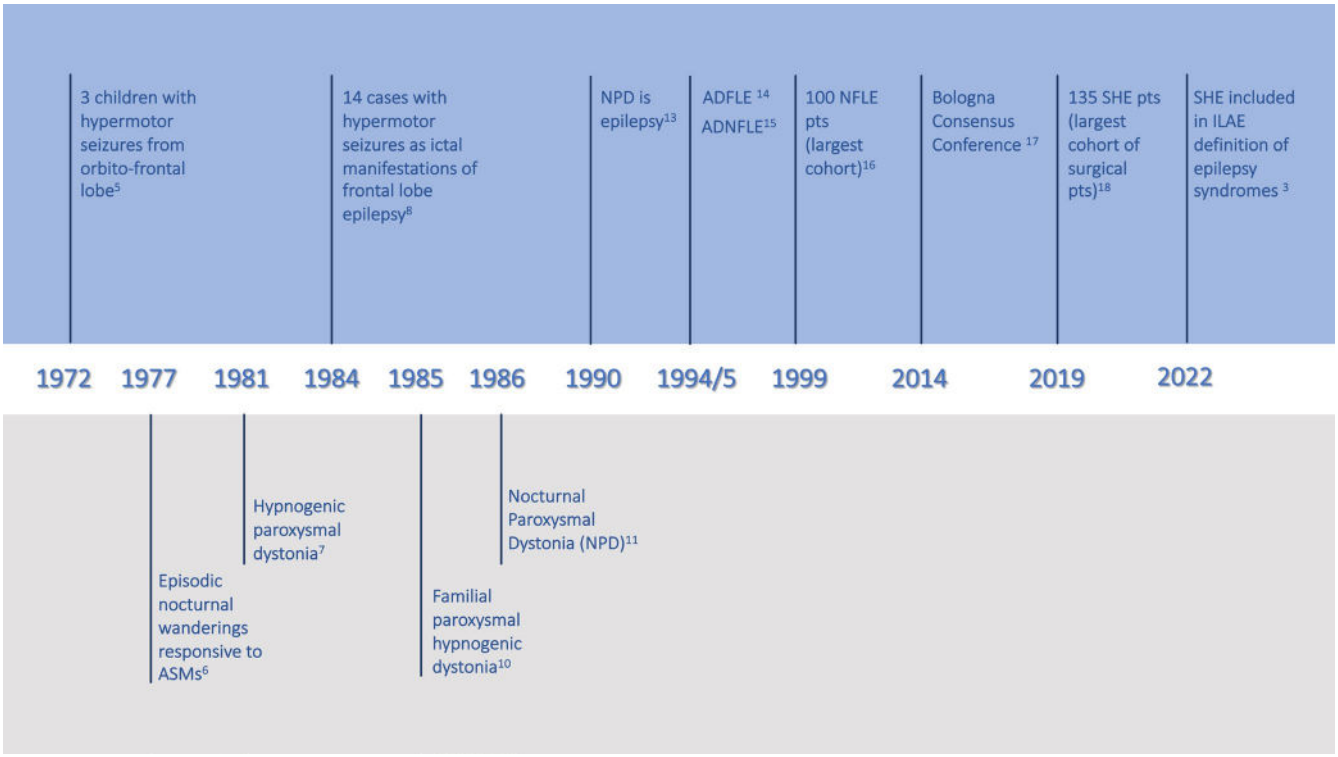

FIGURE 1 Timeline illustrating the key milestones in the evolution from nocturnal paroxysmal dystonia (NPD) to sleep-related hypermotor epilepsy (SHE), highlighting the shifting terminologies and growing understanding of the condition. The gray area represents papers describing sleep-related paroxysmal events of uncertain epileptic origin, whereas the light blu area includes papers and events that document or clarify the epileptic nature of these nocturnal paroxysmal phenomena. ASMs: Anti-seizure medications; ADFLE: Autosomal Dominant Frontal Lobe Epilepsy; ADNFLE: Adosomal Dominant Nocturnal Frontal Lobe Epilepsy; NFLE. Nocturnal Frontal Lobe Epilepsy; pts: patients; ILAE: International League Against Epilepsy.

are studied because they are drug resistant and typically have days or weeks of day and night video-EEG monitoring, and may have lesions. Milder cases, especially those in families, may have a single routine EEG and may be in remission at the time they are evaluated and are typically non-lesional.[15]

The absence of ictal and interictal epileptiform abnormalities does not exclude a diagnosis of SHE, in severe cases (concentrated in surgical series) or milder ones. In surgical series, it is widely recognized that co-registration of the scalp and stereo EEG (SEEG) can show surprisingly little abnormality on scalp EEG even when SEEG is very active (Figure 2).

The authors cite (Figure 2 in ref.[2]) a case with PAs[16] to support their criticism that many of the published NPD cases lacked definitive ictal/interictal epileptiform changes. PAs, frequently occurring in patients with SHE, are characterized by abrupt trunk and limb movements that can resemble simple motor sleep phenomena and exhibit a pseudoperiodic pattern linked to K-complex bursts or Cyclic Alternating Pattern (CAP) recurrence.[1] However, the Consensus Conference deemed PAs insufficient for diagnosing SHE due to their controversial nature, inconsistent nomenclature across SHE study groups, and the risk of unreliable clinical diagnosis when only minor motor events or few episodes are captured.[1,17]

We also note the attempts by Fotedar and Luders to reinterpret EEG tracings from older publications, especially given the challenges of analyzing published figures, rather than the whole recording. We do not wish to address every critique related to interpretations of EEG records from the 1990s, but we want to highlight one specific case—figure 4[2] – which the authors cited as a paradigmatic example of "overreading." Although we will not delve into the objections about this EEG tracing (whose quality understandably falls short of 2024 standards), we would like to point out that the patient in question carried a pathogenic *KCNT1* variant (Figure 2, Family B, subject III.2 in Heron et al.[34]). This patient subsequently underwent epilepsy surgery involving resection of the right mesiolateral frontal region, with histopathology confirming the presence of focal cortical dysplasia (Figure 1, Family B, subject III.2).[35]

Furthermore, the authors propose that epileptic sleep-related paroxysmal motor events require the presence of a magnetic resonance imaging (MRI) lesion (table 1 in ref.[2]). However, even with advances in MRI techniques, 40%–50% of patients with SHE have negative MRIs in surgical series of drug-resistant patients.[18,36]

TABLE 1 Diagnostic criteria for SHE.[17]

Diagnostic certainty	Diagnostic criteria	
Possible SHE	Seizures characterized by significant and disruptive hypermotor events, reported by an *eyewitness*.	
Clinical SHE	*Audio-video documentation* of at least 1 complete hypermotor event, confirmed to be typical by a witness	The recorded episodes must: • be complete, encompassing the onset, evolution, and offset • exclude minor motor events and paroxysmal arousals
Confirmed SHE	*Video-EEG documentation* of hypermotor events recorded during sleep, accompanied by clear-cut epileptic discharges or interictal epileptiform abnormalities	Recordings should be conducted: • during daytime sleep following sleep deprivation, or during a full night's sleep • using at least 19 EEG channels (following the 10–20 International System), along with ECG, oculography, and chin EMG

Note: The absence of clear interictal and ictal EEG correlates, both during wakefulness and sleep, does not preclude the diagnosis of SHE.

Abbreviation: ECG: elelctrocardiogram; EMG: electromyography; SHE: sleep related hypermotor epilepsy.

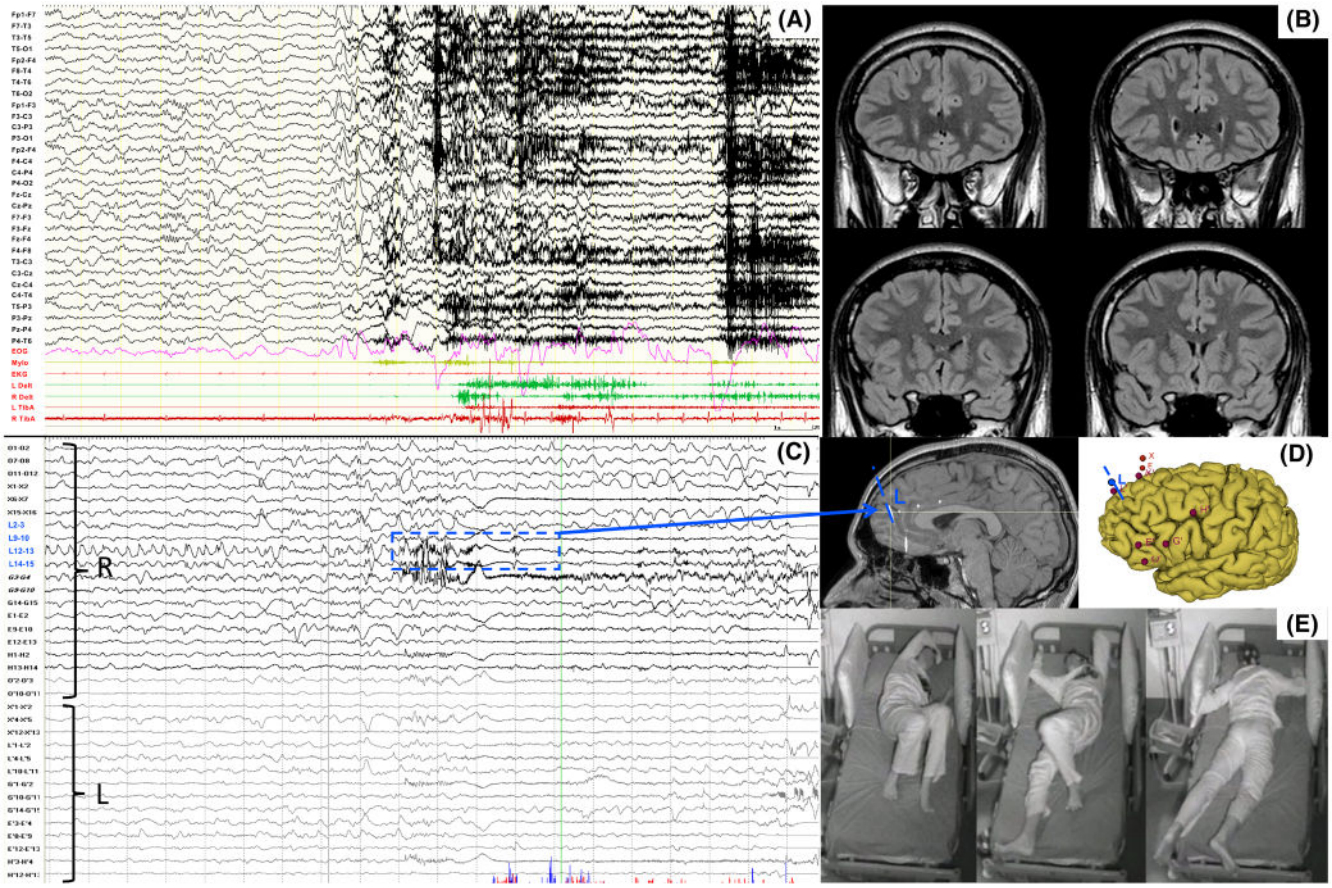

FIGURE 2 This figure summarizes the anatomo-electro-clinical correlation of a patient with right fronto-mesial focal cortical dysplasia IIA with hypermotor seizures during sleep (unpublished case by Nobili Lino). (A) 10–20 scalp EEG recording of a typical seizure showing no clear-cut epileptiform discharge before the movement artifacts. (B) FLAIR MRI was unremarkable, showing no visible focal lesions. (C) Bilateral frontal SEEG implantation showing an ictal discharge associated with a typical hypermotor seizure: A burst of polyspikes and fast discharges are visible over L12-15 and G 3–4 (blue arrow) both exploring the right anterior cingulate gyrus; the activity is then followed by a low-voltage fast discharge tonically involving the same electrodes but also H, E, and X electrodes. (D) MRI and 3D MRI model shows the bilateral implantation scheme and highlights L electrode (blue arrow), which is the most involved electrode in the ictal discharge. (E) Typical ictal semiology consisting of a sudden hypermotor automatism, followed by a fast recovery.

TABLE 2 Genetics of SHE.

Gene	Full name	Location	Inheritance	OMIM number
nAChRs genes[43]	Cholinergic Receptor Nicotinic Alpha 4 Subunit	20q13.33	AD	MIM*118504
CHRNA4	Cholinergic Receptor Nicotinic Beta 2 Subunit	1q21.3	AD	MIM*118507
CHRNB2	Cholinergic Receptor Nicotinic Alpha 2 Subunit	8p21.2	AD	MIM*118502
CHRNA2				
KCNT1[34]	Potassium Sodium-Activated Channel Subfamily T Member 1	9q34.3	AD	MIM*608167
GATOR-1 genes	DEP Domain Containing 5	22q12.2-q12.3	AD	MIM*614191
DEPDC5[44,45]	NPR2- like Protein	3p21.31	AD	MIM*607072
NPRL2[46]	Nitrogen Permease Regulator-like 3	16p13.3	AD	MIM*600928
NPRL3[47]				

Abbreviation: AD, autosomal dominant.

5 | FRONTAL AND EXTRAFRONTAL ORIGIN OF SEIZURES

Fotedar and Luders point out that many of the cases of SHE may have originated outside the frontal lobe. This has been well recognized by many groups and emphasized at the Consensus Conference and, precisely for this reason, led to the change of name from NFLE to SHE.[17] It is well established that up to 30% of patients with hypermotor seizures, once categorized as the hallmark of NFLE, actually have seizures originating from extrafrontal regions.[17] Seizures may arise in areas including the insula,[37] midline parietal cortex,[38] and other regions.[18,39] Therefore, revisiting this well-established point adds little value to their article.

6 | GENETICS

In the initial part of their "critical review," Fotedar and Luders disingenuously imply that the finding of *CHRNA4* pathogenic variants was not replicated. Their review of molecular genetics is outdated, incomplete, and inaccurate. For *CHRNA4*, its pathogenic role in SHE is cemented by identification in both families and de novo cases, in individuals of European, Lebanese, and Japanese ethnicities.[40–42] Multiple groups over the last three decades have confirmed the presence of autosomal dominant pathogenic variants in a range of genes including those encoding nicotinic subunits (*CHRNA4, CHRNB2*, and *CHRNA2*), mechanistic target of rapamycin (mTOR) pathway proteins (*DEPDC5, NPRL2*, and *NPRL3*) and potassium sodium-activated channel subunit (*KCNT1*) (Table 2).[34,43–47] In a series of 103 SHE cases, 19% of familial and 7% of sporadic cases had a pathogenic variant in an established SHE gene.[48] The mTOR pathway genes are sometimes associated with structural malformations visible on MRI and may be included in surgical series.[49,50]

The authors later try to disconnect the molecular findings from the epileptology, implying that these validated genetic variants are associated with non-specific sleep-related paroxysmal motor episodes, rather than with SHE. The clinical relationship of SHE to parasomnias remains poorly understood but, at this time, there is no evidence associating these genes with other familial sleep disorders.[51] There are several reports of patients with pathogenic variants in *CHRNA4*, clinical features of SHE, and ictal epileptiform changes[48] including one case with SEEG documenting a widespread epileptogenic network (case 3[52]). The same findings have been reported for a few patients with germ-line pathogenic variants in the mTOR pathway genes.[53] Overlooking this well-supported evidence disregards significant advancements in understanding the genetic underpinnings of epilepsy.

7 | DO WE NEED OTHER DIAGNOSTIC LABELS?

The authors proposed a four-dimensional classification system for paroxysmal motor sleep episodes based on semiology, naming the new entity "sleep-related paroxysmal motor episodes" (SPME). We believe that this definition lacks both clarity and utility in the terms required by current scientific standards for defining new diagnostic criteria (e.g., prognostic ability, reproducibility, accuracy, and favorable balance between benefits and harms in applying the new definition).[54] The implications of not differentiating epileptic seizures from other sleep-related motor phenomena, resulting in incorrect diagnosis and management, are potentially dangerous in terms of morbidity, mortality risk, and impact on quality of life.

In conclusion, although we certainly welcome continued discourse on SHE, it is important that these discussions be grounded in comprehensive, up-to-date evidence and not a rehash of debates that have long been resolved.

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CONFLICT OF INTEREST STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURES

Francesca Bisulli has served on scientific advisory boards for Jazz, Takeda Pharmaceuticals, Ethypharm, and UCB; has received speaker honoraria from Angelini, UCB, Jazz, and Eisai; has received funding for travel from Jazz, Eisai, Angelini, and UCB; has served as an investigator for UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and Zynerba; and has consulted for Xenon Pharmaceuticals and Takeda Pharmaceuticals.

Samuel F. Berkovic has received unrestricted educational grants to his institution from UCB Pharma, Eisai, SEER, Chiesi, and LivaNova. He has served as a consultant for Praxis Precision Medicines and has received personal honoraria for lectures and presentations from Eisai and DeltaMed. He holds a patent on methods of treatment and diagnosis of epilepsy by detecting mutations in the *SCN1A* gene, which is held by Bionomics Inc. and licensed to Athena Diagnostics and Genetics Technologies Ltd., with institutional royalties. He serves as Chief Medical Officer for the Epilepsy Foundation (Victoria).

Ingrid Scheffer has served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, Takeda Pharmaceuticals, UCB, Xenon Pharmaceuticals, and Longboard Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, LivaNova, Nutricia, Zuellig Pharma, Stoke Therapeutics, Eisai, Akumentis, and Praxis; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, Encoded Therapeutics, Stoke Therapeutics, Eisai, and Longboard Pharmaceuticals; has served as an investigator for Anavex Life Sciences, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc., Epygenyx, ES-Therapeutics, GW Pharma, Longboard Pharmaceuticals, Marinus, Neurocrine BioSciences, Ovid Therapeutics, SK Life Science, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and Zynerba; has consulted for Care Beyond Diagnosis, Epilepsy Consortium, Atheneum Partners, Ovid Therapeutics, UCB, Zynerba Pharmaceuticals, BioMarin, Encoded Therapeutics, Biohaven Pharmaceuticals, Stoke Therapeutics, Praxis; and is a Non-Executive Director of Bellberry Ltd. and a Director of the Australian Academy of Health and Medical Sciences. She may accrue future revenue on a pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics Inc. and licensed to various diagnostic companies; and has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (BFIE) [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012–009).

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed.

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