Clinical and Genetic Features in Patients With Reflex Bathing Epilepsy

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Neurology® 2021;97:e577-e586. doi:10.1212/WNL.0000000000012298

Abstract

Objective
To describe the clinical and genetic findings in a cohort of individuals with bathing epilepsy, a rare form of reflex epilepsy.

Methods
We investigated by Sanger and targeted resequencing the SYN1 gene in 12 individuals from 10 different families presenting with seizures triggered primarily by bathing or showering. An additional 12 individuals with hot-water epilepsy were also screened.

Results
In all families with bathing epilepsy, we identified 8 distinct pathogenic or likely pathogenic variants and 2 variants of unknown significance in SYN1, 9 of which are novel. Conversely, none of the individuals with hot-water epilepsy displayed SYN1 variants. In mutated individuals, seizures were typically triggered by showering or bathing regardless of the water temperature. Additional triggers included fingernail clipping, haircutting, or watching someone take a shower. Unprovoked seizures and a variable degree of developmental delay were also common.

Conclusion
Bathing epilepsy is genetically distinct reflex epilepsy caused mainly by SYN1 mutations.

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Reflex epilepsies (REs) refer to conditions characterized by recurrent seizures triggered primarily by specific motor, sensory, or cognitive stimulation. Acquired or genetic etiologic factors are believed to underlie complex and largely unknown pathophysiologic mechanisms that ultimately lead to hyperexcitability of cortical or subcortical neuronal areas in response to physiologic stimuli. The genetic background of REs is highly heterogeneous, and only a few causative genes have been identified in humans.

Hot-water epilepsy (HWE) and bathing epilepsy (BE) are among the most common REs in the pediatric population and are considered part of the same spectrum. However, recent evidence suggests that they are different entities with distinct genetics, triggers (hot vs pouring water), clinical presentation, and comorbid conditions. Indeed, autosomal dominant pedigree with reduced penetrance allowed mapping 2 loci for HWE at chromosomes 10q21.3-q22.3 and 4q24-q28, and affected children have otherwise normal development. Conversely, BE has been associated with mutations in the X-linked gene SYN1 that encodes 1 of the 3 Synapsins (SYN1–SYN3), a family of phosphoproteins involved in synaptic development, function, and plasticity. In addition to seizures triggered by water, SYN1 mutations are responsible for a wide range of neurodevelopmental disorders, including cognitive impairment, autism spectrum disorders (ASD), and unprovoked seizures. To date, SYN1 mutations have been described in 9 patients with BE and 1 patient with HWE.

We report the clinical and genetic findings of 12 individuals from 10 unrelated families affected by BE, all bearing variants in SYN1. The comprehensive analysis of our large cohort and additional cases reported in the literature indicate that BE is a genetically homogeneous distinct RE having SYN1 as its major causative gene.

Methods

Study Design and Participant Recruitment
We enrolled 21 previously unreported probands from 10 unrelated families (figure 1A) with RE induced by showering or bathing through the Network Therapy of Rare Epilepsies. We included patients with bathing/showering-induced seizures documented via either video-EEG or home video recordings by the parents. Clinical data, including genetic findings, neurodevelopmental performance, epilepsy phenotype, and treatment response, were collected with an anonymized, electronic questionnaire. Interictal/ictal (video-)EEG recordings, brain MRI, and neuropsychological tests were centrally reviewed. The neuropsychological and behavioral evaluation was assessed by the Wechsler Intelligence Scale for Children-IV, Wechsler Preschool and Primary Scale of Intelligence-III, Autism Diagnostic Observation Schedule, and Griffiths Mental Development Scale–Extended Revised.

Genetic Investigations
Genomic DNA was isolated from leukocytes of peripheral blood by the use of standard protocols. Target genetic analysis of SYN1 was performed by Sanger sequencing in individuals of families 1 through 4, 7, and 8. Other individuals were investigated either by epilepsy gene panels (families 6, 10) or whole-exome sequencing (families 5, 9), and identified variants were confirmed by Sanger sequencing (additional details about sequencing process and data analysis are available in supplemental data, doi.org/10.5061/dryad.w0vt4b8qr). Variants were classified according to the American College of Medical Genetics and Genomics guidelines. In parallel, we screened for SYN1 mutations in a previously reported cohort of 21 patients with HWE to gain further insights into genotype-phenotype correlations of water-related REs.

Standard Protocol Approvals, Registrations, and Patient Consents
Ethics approval from the IRCCS “G. Gaslini” Institute (Genova, Italy) was obtained for this study. We received written informed consent from all patients (or guardians of patients) participating in this study and authorization for disclosure (consent-to-disclose) of any recognizable persons in photographs and videos.

Data Availability
Supplemental data, including clinical descriptions, methods of genetic testing, EEGs, and tables of previously reported cases with BE and HWE, are available on Dryad (doi.org/10.5061/dryad.w0vt4b8qr). Videos are available on the Neurology® website.

Additional anonymized data that support the findings of this study are available from the corresponding author (P.S.) on reasonable request. Not all of the data are publicly available because they contain information that could compromise children’s privacy and family consent.

Results

Clinical Findings
The demographic and clinical features of our patients are summarized in table 1. Extensive clinical details are available in the supplemental data (doi.org/10.5061/dryad.w0vt4b8qr). All but 2 individuals (II:3 from family 5, II:1 from family 9) were males. All affected individuals had focal epilepsy with
impaired awareness triggered by the experience of bathing or showering, regardless of water temperature. Seizures were typically triggered by pouring water over the head and consisted of behavioral arrest associated with pallor, cyanotic lips, buccal automatisms, and transient hypotonia (supplemental data and videos). Evolution to bilateral tonic-clonic seizures was clearly described in 4, and loss of consciousness was reported in 1 individual. In 2 individuals, seizures were also triggered by rubbing with a towel after showering (supplemental data, video 1). Seizures also occurred in 1 individual while washing hands and during the immersion of feet in the water, including seawater (II:1, family 1). Moreover, 2 patients also experienced a bilateral tonic-clonic seizure while watching their relatives take a shower or by the thought of bathing/showering (II:1, family 1; II:1, family 6). One adult (IV:2, family 10) had an improvement in seizure control after predominantly showering rather than bathing in warm water. Additional triggers were fingernail clipping in 2 individuals (II:1, family 6; II:1, family 8), 1 of whom also experienced seizures provoked by haircutting (II:1, family 6). The age at onset of provoked seizure ranged from 8 months to 15 years, with weekly to monthly frequency.

Nine participants also developed unprovoked seizures, including focal to bilateral tonic-clonic nocturnal seizures with autonomic features in 5 individuals. Three individuals reported febrile seizures, occurring before the onset of provoked seizures in 2 of them. One additional individual (II:3, family 5) had no provoked focal seizures before the onset of BE.

All individuals received antiseizure medications. Half of them had a satisfactory response mainly to clobazam or valproic acid, and 3 achieved complete control of seizures.

Ictal EEG recording showed high-voltage polymorphic theta activity over the frontal-temporal areas in 2 participants (figure 2). Interictal findings in other participants are available in the supplemental data (figures e-1 and e-2, doi.org/10.5061/dryad.w0vt4b8qr). Brain MRI was performed in 10 of the 13 participants with unremarkable findings.
| Family 1 | Family 2 | Family 3 | Family 4 | Family 5 | Family 6 | Family 7 | Family 8 | Family 9 | Family 10 |
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| II:1    | II:1    | II:1    | II:2    | II:1    | II:2    | II:3    | II:4    | II:1    | II:2    |
| Age, sex| 18 y M  | 3 y M   | 9 y M   | 15 y M  | 2.5 y M | 2.5 y M | 7 y F   | 5.5 y M | 2 y M   | 13 y M  |
| SYN1 variant (NM_006950.3) | c.1264C>T p.(Arg422*) | c.1439dupC p.(Leu481fs202*) | c.436-1G>C | c.1406dupA p.(Pro470Alafs*214) | c.1472_1473insT p.(Gln491Hisfs*193) | c.929C>A p.(Ala310Asp) | c.1647_1650dupCGCC p.(Ser551Argfs*134) | c.1647_1771dup p.(Arg587, Pro590dup) | c.1266delA |
| Detection analysis/Segregation | Sanger sequencing | De novo | Sanger sequencing Maternal | Sanger sequencing Maternal | WES Maternal | Gene panel Maternal | Sanger sequencing Maternal | WES Maternal | Gene panel Presumed maternal |
| FH of BA | No | Yes, maternal uncle | No | Yes, sister | Yes, sister | Yes, brothers | No | No | Yes, maternal aunt | Yes, 7 maternal male relatives |
| Development | Speech delay, aggressive behavior, ADHD | Speech delay, hyperactivity | GDD, moderate ID, ASD, motor stereotypies, aggressive behavior, echolalia | Normal | Mild GDD, speech delay, ADHD | Mild GDD, speech delay, autonomic features | GDD, moderate ID, ASD, ADH | Normal | GDD, mild ID, ASD, motor stereotypies ADHD | Mild GDD, speech delay, mild ID, autistic traits |
| Age at RE onset | 5 y 2 y 7 y 8 y 22 mo 14 mo 2 y 4 y 7 mo 1 y 3 mo | 8 mo 8 mo 15 y |
| RE onset | After showering, rubbing with towel, watching his sister having a shower | During or after bathing | During or after showering, rubbing with towel | During bathing (pouring water over the head) | During bathing | During bathing | After bathing/showering, haircutting, fingernail clipping, watching someone while bathing, idea of bathing | During or after bathing, hair washing | During bathing/showering, fingernail clipping | During or after bathing/showering, during immersion of the feet in water and during febrile events illnesses |
| Features | Impaired awareness, pallor, cyanosis, oral automatisms, hypotonia | Impaired awareness, lip cyanosis, buccal automatisms, hyperpnoea | Impaired awareness, buccal automatisms, lip cyanosis, hypersalivation, hypotonus | Impaired awareness, lip cyanosis, focal to bilateral TCS | Impaired awareness, focal to bilateral TCS | Impaired awareness, focal to bilateral TCS | Focal with impaired awareness | Autonomic seizures with apnea, cyanosis, loss of consciousness, automatisms | Autonomic features, atonic seizures, pallor, staring, cyanosis | Autonomic seizures with apnea, smacking, salivation, cyanosis | Autonomic seizures, fixed gaze, pausing, myoclonus, pallor, cyanosis, orobuccal automatisms | Focal impaired awareness, orolingual automatism, salivation and spitting, right hand tapping, leftward head and gaze, disorientation with automatisms (e.g., whistling and kissing) |
| Seizure frequency at the onset | Weekly | Monthly | 1–2/wk | Weekly | Weekly | Weekly | Weekly | 2–8/mo | 1–2/wk | 2–3/wk | 2–3/wk | 1–2/wk |
Table 1 Genetic and Phenotypic Features of Subjects With SYN1 Variants and BE (continued)

|               | Family 1 | Family 2 | Family 3 | Family 4 | Family 5 | Family 6 | Family 7 | Family 8 | Family 9 | Family 10 |
|---------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|-----------|
| Febrile seizure | Yes (4 y 9 mo) | No | No | No | No | No | No | Yes (3 y) | No | No | Yes, between 9 and 18 mo |
| Other seizures | Nocturnal TCS at 6 y | No | No | No | Focal impaired awareness seizures, 2.5 y | Focal impaired awareness seizures, 2 y | Focal impaired awareness seizures, 9 mo | Nocturnal autonomic seizures, at 5y | Nocturnal autonomic seizures, 1 y 3 mo | Infantile spasms, 8 mo; TCS with automatism, 2 y; atonic atypical absence seizures |
| EEG interictal | R temporal, L anterior temporal | L frontotemporal | R central, temporal | Normal | Bilateral temporal | Bilateral temporal | Theta activity over the right temporal regions | Bilateral centrotemporal | Normal | R and L temporal |
| Ictal | NA | NA | NA | NA | NA | NA | Rhythmic theta seizure pattern right temporal | Rhythmic theta seizure pattern right temporal | Rhythmic theta left temporal | Beta diffuse | NA |
| ASMs | CLB, VPA | CLB, VGB, CBZ, CLB | CLB | NA | VPA | VPA | VPA | VPA, STM, LTG | CBZ | OXC, STM, VPA, LTG | CBZ, LTG, VPA |
| Response to medications | Decreased seizures frequency | Partial response | Decreased seizures frequency | NA | Poor response | Poor response | Seizure-free | No | Seizure-free, avoidance of warm water | Seizure-free, avoidance of warm water (CBL, RUF, BRV) | Decreased seizure frequency (CBL, RUF, BRV) | VPA and avoidance of warm water on his feet |

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = antiseizure medication; BE = bathing epilepsy; BRV = brivaracetam; CBZ = carbamazepine; CLB = clobazam; FH = family history; GDD = global developmental delay; GTCS = generalized tonic-clonic seizures; ID = intellectual disability; KD = ketogenic diet; LAC = lacosamide; LEV = levetiracetam; LTG = lamotrigine; NA = not available; OXC = oxcarbazepine; RE = reflex epilepsy; RUF = rufinamide; SE = status epilepticus; STM, sulthiame; TCS = tonic-clonic seizures; VGB = vigabatrin; VPA = valproic acid; WES = whole-exome sequencing; ZNS = zonisamide.

Vagus nerve stimulator was also placed, resulting in a further decrease in the frequency of unprovoked seizures but not affecting bathing seizures.
All but 2 participants (II:1, family 4; II:1, family 7) had a delay and cognitive impairment. Specifically, 8 individuals had a global developmental delay (GDD), and 5 of them were found to have intellectual disability that ranged from mild to severe. Of note, 6 participants were diagnosed with attention-deficit/hyperactivity disorder, and 1 individual had hyperactivity. Three participants had ASD. Behavioral issues such as aggressive behavior were noticed in 2 participants. One adult (IV:2, family 10) now lives and works with minimal support. The clinical features of 21 patients with HWE are summarized in table e-1 (doi.org/10.5061/dryad.w0vt4b8qr). Twenty participants had focal seizures, 8 of whom also developed focal to bilateral seizures. Unprovoked seizures occurred in 62% of cases. Seizure activity was recorded mainly over unilateral temporal regions. Seizure control was achieved by reducing the temperature and duration of the bath or shower and by antiseizure medications such as carbamazepine.10

Genetic Findings
We identified 8 distinct pathogenic variants in SYN1 (NM_006950.3) c.1264C>T p.(Arg422*) in case II:1 of family 1; c.1439dupC p.(Leu481fs202*) in case III:1 of family 2; c.774+2T>C in case II:1 of family 3; c.436 -1G>C in case II:1 of family 4; c.1406dupA p.(Pro470Alafs*214) in cases II:1, II:2, and II:3 of family 5; c.1472_1473insT p.(Gln491Hisfs*193) in case II:IV of family 6; c.1647_1650dupCGCC p.(Ser551Argfs*134) in case II:1 of family 8; c.1266delA p.(Gln423Serfs*244) in case II:2 of family 10; and 2 variants of unknown significance [c.929C>A p.(Ala310Asp) in case II:3 of family 7; c.1760_1771dup p.(Arg587_Pro590dup) in case II:2 of family 9] (table 1 and figure 1B). All variants were absent in the gnomAD database. The c.1264C>T p.(Arg422*) variant, previously reported,18 occurred de novo, while all other variants were novel and maternally inherited or presumed to be maternally inherited in family 10. The c.436-1G>C and c.774+2T>C variants are predicted to severely affect the protein structure through aberrant mRNA splicing. The c.1264C>T p.(Arg422*) is predicted to undergo nonsense-mediated mRNA decay or result in a truncated protein. All the frameshift variants [c.1439dupC p.(Leu481fs202*), c.1406dupA p.(Pro470Alafs*214), c.1472_1473insT p.(Gln491Hisfs*193), c.1647_1650dupCGCC p.(Ser551Argfs*134) and c.1266delA p.(Gln491Hisfs*134)] lead to new reading frames predicted to give rise to a truncated or degraded protein. Although the missense c.929C>A p.(Ala310Asp) and the in-frame insertion c.1760_1771dup p.(Arg587_Pro590dup) variants are classified as variants of unknown significance, they are predicted to have a deleterious effect by multiple in silico analysis and evolution conservation tools. The clinical association with BE further supports their likely pathogenic role. Whole-exome sequencing failed to identify additional pathogenic or likely pathogenic variants in any other Online Mendelian Inheritance in Man genes in all tested individuals. No pathogenic or likely pathogenic variants in SYN1 were identified in the HWE cohort.
Discussion

In the first original description of SYN1 family, it was mentioned the occurrence of water-induced seizures in a patient carrying the p.(W356*) SYN1 variant. However, since the first report of 7 individuals belonging to the same large French-Canadian family carrying the truncating variant p.(Gln555*), only 2 additional individuals harboring distinct nonsense p.(Arg422*) and missense p.(Ile319Thr) variants in SYN1 have been described (table e-2, doi.org/10.5061/dryad.w0vt4b8qr). All patients had reflex seizures triggered by bathing or showering and variable neurodevelopmental disorders ranging from dyslexia or specific language impairments to pervasive developmental disorders. Here, we describe the largest cohort of patients with BE carrying SYN1 mutations.

Apart from the previously reported nonsense c.1264C>T p.(Arg422*) variant, all other identified alleles are novel and include 2 splicing-site, 5 distinct frameshift, 1 missense, and 1 in-frame insertion variants (figure 1B). The nonsense, frameshift, and splicing variants are predicted to act through a loss-of-function mechanism like most SYN1 mutations linked to BE. Although we did not functionally assess the impact of the missense and in-frame variants, they affect the highly conserved residue of the protein and are located in important functional domains. Overall, SYN1 variants related to BE are clustered in the Pro-rich regulatory domain, while the few variants not associated with BE are also found in other protein domains. However, given the limited number of individuals reported so far, further studies are needed to corroborate this observation and to provide further insights into the genotype-phenotype correlations (figure 1B). Moreover, we observed intrafamilial variability as pointed out by the segregation analysis in family 2 in which the maternal uncle displayed unprovoked seizure and ASD but not BE. This is in line with the previous evidence suggesting that all individuals harboring SYN1 mutations have variable neurodevelopmental impairments yet not all develop BE.

The main clinical features of our cohort are consistent with the core phenotype of BE (table 1). All but 1 individual presented with seizures provoked by bathing or bathing regardless of water temperature. One individual experienced recurrent seizures provoked by immersion of feet in water, not by pouring of water over the head. Additional triggers were rubbing with a wet towel, fingernail cutting, and haircutting in some individuals. In 2 individuals, seizures were also provoked by watching someone taking a bath or just thinking about having a bath.

Of note, we report the first 2 female individuals with BE. They also displayed a variable degree of developmental delay, from mild GDD to severe cognitive impairment associated with unprovoked seizures. We hypothesize that skewed X-inactivation occurring in the brain tissues could explain the expression of the disease in these female carriers. Nine of the 13 participants also developed unprovoked seizures. In 2 of them, febrile seizures preceded the onset of bathing seizures. Other unprovoked seizures occurred at night in 5 participants and were mostly focal or focal to bilateral with autonomic features. Only 1 individual had a prolonged seizure resulting in status epilepticus.

Antiseizure treatment was required in all participants, and partial or complete control of seizures was achieved in 6 cases. Clobazam and valproic acid were the most effective drugs. Ictal EEG recorded in 2 participants showed rhythmic theta activity over the frontocentral/temporal regions, in keeping with the previous reports. Variable cognitive impairment was noticed in 10 of 13 participants. ASD, attention-deficit/hyperactivity disorder, and behavioral issues were also predominant features in several participants.

Overall, the clinical and electrophysiologic findings in our patients overlap those described in previous BE cases, suggesting that this condition is a specific and preventable RE related to contact with water.

SYN1 encodes a neuron-specific phosphoprotein implicated in the regulation of neurotransmitter release and synaptogenesis. Its role in epilepsy has been elucidated by studies in the SYN1 knockout mouse model showing impaired synaptic vesicle trafficking and impairment of GABA release through a loss-of-function mechanism that results in higher network excitability and firing activity. Although the exact pathophysiology of SYN1-related BE is currently unknown, the ictal SPECT findings in some individuals have suggested insular cortex involvement. Indeed, the insula is a key integrative multisensory area, well connected with the temporal lobe and potentially able to generate motor and autonomic symptoms, like those observed in BE cases, if functionally perturbed by genetic mutations. Accordingly, SYN1 mutations may lead to imbalances between excitatory and inhibitory influences at the synaptic level, thus entraining temporal and insular areas into a seizure activity after water pouring.

REs represent a spectrum of conditions characterized by broad clinical and genetic heterogeneity and several overlapping features. Apart from SYN1, a few additional RE-related genes have been reported, including SYNAP1 in individuals with chewing reflex, CDKL5-related disorders exhibiting diaper change reflex, SCN1A in somatosensory reflex seizures, and CHD2 in photosensitive seizures. It is likely that in all these epilepsy types, the genetic defect eventually results in abnormal hyperexcitability of cortical areas that are physiologically activated during specific sensory stimulation, acting as triggers.

The recent report of HWE in an individual carrying a splice variant (c.527+1G>T) in SYN1 may argue whether BE and HWE belong to the same phenotypic spectrum. Thus, to specifically address this issue, we screened a cohort of cases
showing HWE and found no evidence of pathogenic variants in SYN1.

HWE, largely reported in southern India, is induced by bathing with hot water usually $>37^\text{\circ}C$.29 Seizures often occur when individuals are seated and hot water is poured from a washtub or basin over their heads.10,29 Seizures may also start with self-induction in some patients as they enjoy this situation. Similar to BE, there is a male-to-female predominance, and $\approx20\%$ to $40\%$ of individuals with HWE may develop spontaneous seizures,8 but unlike those with BE, the majority of individuals have normal development. Several studies, including EEG and fMRI, have suggested a predominant temporal lobe involvement, with the possible contribution of parietal and occipital areas.10,31 SPECT studies have demonstrated ictal hypermetabolic uptake in the medial temporal structures and hypothalamus.32 Although the physiopathology of HWE remains unknown, it has been suggested that it could be related to a hyperthermic kindling involving the thermoregulation center of the hypothalamus that triggers seizures.33,34

Despite a similar ictal semiology and EEG, our data suggest that BE and HWE are likely distinct epileptic disorders with different genetics, seizure triggers (pouring vs hot water), and hyperexcitability of cortical circuits. The improvement observed after decreasing water temperature in HWE33 and the report of a few individuals with BE who also experienced seizure precipitated by rubbing the face with a wet cloth or nail clipping17 further support our thoughts. Similarly, 2 of our patients also experienced seizures triggered by rubbing with a towel after showering. The other 2 individuals had seizures triggered by fingernail clipping and one of them also by haircutting. Taken together, these findings suggest that BE is intrinsically related to a somatosensory stimulus rather than the simple water temperature, as instead observed in HWE. Hence, it may be possible that the reflex seizure reported in 2 SYN1 cases, apparently after hot water exposure, was instead precipitated by the somatosensory stimulus of water, and the temperature played only a confounding role. Moreover, the report of 2 individuals with seizures provoked by watching someone bathing or showering suggests that the pathophysiology of SYN1-related RE could be even more complex, likely involving mirror-like activities and yet unknown and tightly regulated neuronal circuits.

Recent simulation theories in cognitive neuroscience emphasize that sensorimotor capacities and cognitive processes are inseparable because the simulation process involves the same sensorimotor neural correlates that are active during the action execution or interaction with the actual object or entity itself.35 Accordingly, watching someone else bathing or showering or imagining bathing or showering may involve the same neuronal circuits that trigger the seizure when acting.

BE is a clinically and genetically homogeneous distinct RE and should be considered a handle for the molecular diagnosis of SYN1-related epilepsy. Early identification of the molecular defect may help start early intervention strategies to optimize function and quality of life and to prevent comorbid conditions in affected patients. Future studies using advances in electrophysiology and imaging data acquisition will help to define the genotypic-phenotypic spectrum and understand the underlying pathomechanisms of this rare RE to eventually develop effective and targeted therapeutic strategies.

**Acknowledgment**

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018-2022 (legge 232 del 2016).

**Study Funding**

This research was funded in whole, or in part, by the Welcome Trust [203914/Z/16/Z]. This work has been supported by the Italian Ministry of Health (grant RF-2016-02361949 to F. Zara).

**Disclosure**

P. Scudieri has received speaker fees; participated in advisory boards for Biomarin, Zogenyx, and GW Pharmaceuticals; and has received research funding by ENECTA BV, GW Pharmaceuticals, Kolfsarma Srl, and Eisai. R.H. Thomas has received honoraria from Arvelle, Eisai, GW Pharma, Sanofi, UCB Pharma, and Zogenix and meeting support from Bial, LivaNova, and Novartis. G.C. Wohlrab obtained honoraria for speaking engagements from Desitin (Hamburg, Germany) and Novartis (Nürnberg, Germany). He gave scientific advice for PTC Therapeutics (Frankfurt, Germany). The other authors do not report any conflict of interest. Go to Neurology.org/N for full disclosures.

**Publication History**

Received by Neurology December 21, 2020. Accepted in final form May 5, 2021.
Appendix (continued)

| Name                        | Location                                      | Contribution                                                                 |
|-----------------------------|-----------------------------------------------|-------------------------------------------------------------------------------|
| Michele Iacomino, PhD       | Istituto Giannina Gaslini, Genoa, Italy       | Genetic analysis, data analysis                                               |
| Antonella Riva, MD          | Istituto Giannina Gaslini, Genoa, Italy       | Patient recruitment, clinical assessment, final revision of the manuscript    |
| Barbara Carlini, MSc        | Istituto Giannina Gaslini, Genoa, Italy       | Genetic analysis                                                              |
| Letizia Camerota, MD        | University of L’Aquila, Italy                 | Patient recruitment, clinical assessment, final revision of the manuscript    |
| Vincenzo Belcastro, MD      | Neurology Unit, Maggiore Hospital, ASST-Lodi, Lodi, Italy | Patient recruitment, clinical assessment, final revision of the manuscript    |
| Paolo Prontera, MD, PhD     | Medical Genetics Unit, “S. Maria della Misericordia” Hospital, Perugia, Italy | Patient recruitment, clinical assessment, final revision of the manuscript    |
| Vincenzo Salpietro, MD      | Istituto Giannina Gaslini, Genoa, Italy       | Recruitment of patients with HWE                                               |
| Paolo Scudieri, PhD         | Istituto Giannina Gaslini, Genoa, Italy       | Genetic testing                                                               |
| Simona Baldassari, PhD      | Istituto Giannina Gaslini, Genoa, Italy       | Genetic testing                                                               |
| Vincenzo Salpietro, MD      | Istituto Giannina Gaslini, Genoa, Italy       | Patient evaluation, clinical assessment, final revision                       |
| Giuseppe Novelli, PhD       | Tor Vergata University of Rome, Italy         | Genetic testing                                                               |
| Chiara De Luca, MD          | Human Genetics, Department of Life, Health and Environmental Sciences, University of L’Aquila, Italy | Patient recruitment, clinical assessment, final revision of the manuscript |
| Celina von Stulpnagel, MD   | Department of Pediatrics, University Hospital Munich, Germany | Patient recruitment, clinical assessment, final revision of the manuscript |
| Felicitas Kluger, MD        | Epilepsy Center for Children and Adolescents, Vogtareuth, Germany | Drafting and revision of the manuscript                                      |
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References

1. Okudan ZV, Ozkara Ç. Reflex epilepsy: triggers and management strategies. Neuro-psychiatr Dis Treat. 2018;14:327-337.
2. Striano S, Coppola A, del Giudice L, Striano P. Reflex seizures and reflex epilepsies: old models for understanding mechanisms of epileptogenesis. Epilepsy Res. 2012; 100(1-2):1-11.
3. Koop M, Caciagli L, Pressler RM, Lehnertz K, Beniczky S. Reflex seizures, traits, and epilepsies: from physiology to pathology. Lancet Neurol. 2016;15(1):92-105.
4. Micheliucci R, Mecarelli O, Bove G, et al. A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures. Neurology. 2007;68(24):2150-2151.
5. Galizia EC, Myers CT, Leu C, et al. CHD2 variants are a risk factor for photosensitivity in epilepsy. Brain. 2015;138(pt 5):1198-1207.
6. Italiano D, Striano P, Russo E, et al. Genetics of reflex seizures and epilepsies in human and animals. Epilepsy Res. 2016;121:77-84.
7. Vlaskamp DRM, Shaw BJ, Burgess R, et al. SYNGAP1 encephalopathy: a distinctive generalized developmental and epileptic encephalopathy. Neurology. 2019;92(2):e96-e107.
8. Zeki G, Iker IH, Hidir UA, Zeki O. Hot water epilepsy: seizure type, water temperature, EEG findings and treatment. Neurologist. 2010;16(2):109-112.
