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# Clinical and Genetic Features in Patients With Reflex Bathing Epilepsy

Andrea Accogli, MD,\* Gert Wiegand, MD,\* Marcello Scala, MD, Caterina Cerminara, MD, Michele Iacomino, PhD, Antonella Riva, MD, Barbara Carlini, MSc, Letizia Camerota, MD, Vincenzo Belcastro, MD, Paolo Prontera, MD, PhD, Alberto Fernández-Jaén, MD, PhD, Nerses Bebek, MD, PhD, Paolo Scudieri, PhD, Simona Baldassari, PhD, Vincenzo Salpietro, MD, Giuseppe Novelli, PhD, Chiara De Luca, MD, Celina von Stülpnagel, MD, Felicitas Kluger, MD, Gerhard Josef Kluger, MD, Gabriele Christine Wohlrab, MD, Georgia Ramantani, MD, David Lewis-Smith, MClInRes, MRCP, Rhys H. Thomas, PhD, FRCP, Ming Lai, MBBS, Alberto Verrotti, MD, PhD, Salvatore Striano, MD, Christel Depienne, PhD, Carlo Minetti, MD, PhD, Fabio Benfenati, MD, PhD, Francesco Brancati, MD, PhD, Federico Zara, PhD, and Pasquale Striano, MD, PhD

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## Correspondence

Dr. Striano  
pasqualestriano@gaslini.org  
or Dr. Zara  
federicozara@gaslini.org

## 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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\*These authors contributed equally to this work.

From IRCCS Istituto Giannina Gaslini (A.A., M.S., M.I., A.R., B.C., P.S., S.B., V.D.S., C.M., F.Z., P.S.); Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI) (A.A., M.S., P.S., V.D.S., C.M., F.Z., P.S.), University of Genoa, Italy; Neuropediatrics Section of the Department of Pediatrics (G.W.), Asklepios Clinic Hamburg Nord-Heidelberg, Hamburg; Department of Pediatric and Adolescent Medicine II (Neuropediatrics, Social Pediatrics) (G.W.), University Medical Centre Schleswig-Holstein, Kiel, Germany; Department of Neurosciences (C.C., C.D.L.), Pediatric Neurology Unit, Tor Vergata University, Roma; Human Genetics (L.C., F. Brancati), Department of Life, Health, and Environmental Sciences, and Department of Pediatrics (A.V.), University of L'Aquila; Child Neuropsychiatry Unit (V.B.), Department of Mental Health, ASST-LARIANA, Como; Medical Genetics Unit (P.P.), "S. Maria della Misericordia" Hospital, Perugia, Italy; Department of Pediatric Neurology (A.F.-J.), Hospital Universitario Quirónsalud and Universidad Europea de Madrid, Madrid, Spain; Istanbul University Istanbul Faculty of Medicine (N.B.), Department of Neurology, Turkey; Department of Biomedicine and Prevention (G.N.), Tor Vergata University of Rome; IRCCS Neuromed (G.N.), Pozzilli, Italy; Department of Pharmacology (G.N.), School of Medicine, University of Nevada, Reno; Department of Pediatrics (C.v.S.), University Hospital Munich, Germany; Paracelsus Medical University (C.v.S.), Salzburg, Austria; Epilepsy Center for Children and Adolescents (F.K., G.J.K.), Vogtareuth, Germany; Department of Neuropediatrics (G.C.W., G.R.), University Children's Hospital Zurich, Switzerland; Translational and Clinical Research Institute (D.L.-S., R.H.T., M.L.), Newcastle University; Department of Clinical Neurosciences (D.L.-S., R.H.T., M.L.), Newcastle Upon Tyne Hospitals National Health Service Foundation Trust, UK; Epilepsy Center (S.S.), Federico II University, Napoli, Italy; Institute of Human Genetics (C.D.), University Hospital Essen, University of Duisburg-Essen, Essen, Germany; Institut du Cerveau et de la Moelle épinière (ICM) (C.D.), Sorbonne Université, UMR S 1127, Inserm U1127, CNRS UMR 7225, Paris, France; Center for Synaptic Neuroscience and Technology (F. Benfenati), Istituto Italiano di Tecnologia; IRCCS Ospedale Policlinico San Martino (F. Benfenati), Genoa; and Human Functional Genomics (F. Brancati), IRCCS San Raffaele Pisana, Rome, Italy

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## Glossary

ASD = autism spectrum disorder; BE = bathing epilepsy; GDD = global developmental delay; HWE = hot-water epilepsy; RE = reflex epilepsy; SYN = Synapsin.

Reflex epilepsies (REs) refer to conditions characterized by recurrent seizures triggered primarily by specific motor, sensory, or cognitive stimulation.<sup>1,2</sup> 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.<sup>3</sup> The genetic background of REs is highly heterogeneous, and only a few causative genes have been identified in humans.<sup>4-7</sup>

Hot-water epilepsy (HWE) and bathing epilepsy (BE) are among the most common REs in the pediatric population<sup>8,9</sup> and are considered part of the same spectrum.<sup>10</sup> 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<sup>11</sup> and 4q24-q28,<sup>12</sup> 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.<sup>13,14</sup> 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.<sup>15,16</sup> To date, *SYN1* mutations have been described in 9 patients with BE<sup>17-19</sup> and 1 patient with HWE.<sup>20</sup>

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.<sup>21</sup> In parallel, we screened for *SYN1* mutations in a previously reported<sup>10</sup> 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*<sup>®</sup> website.

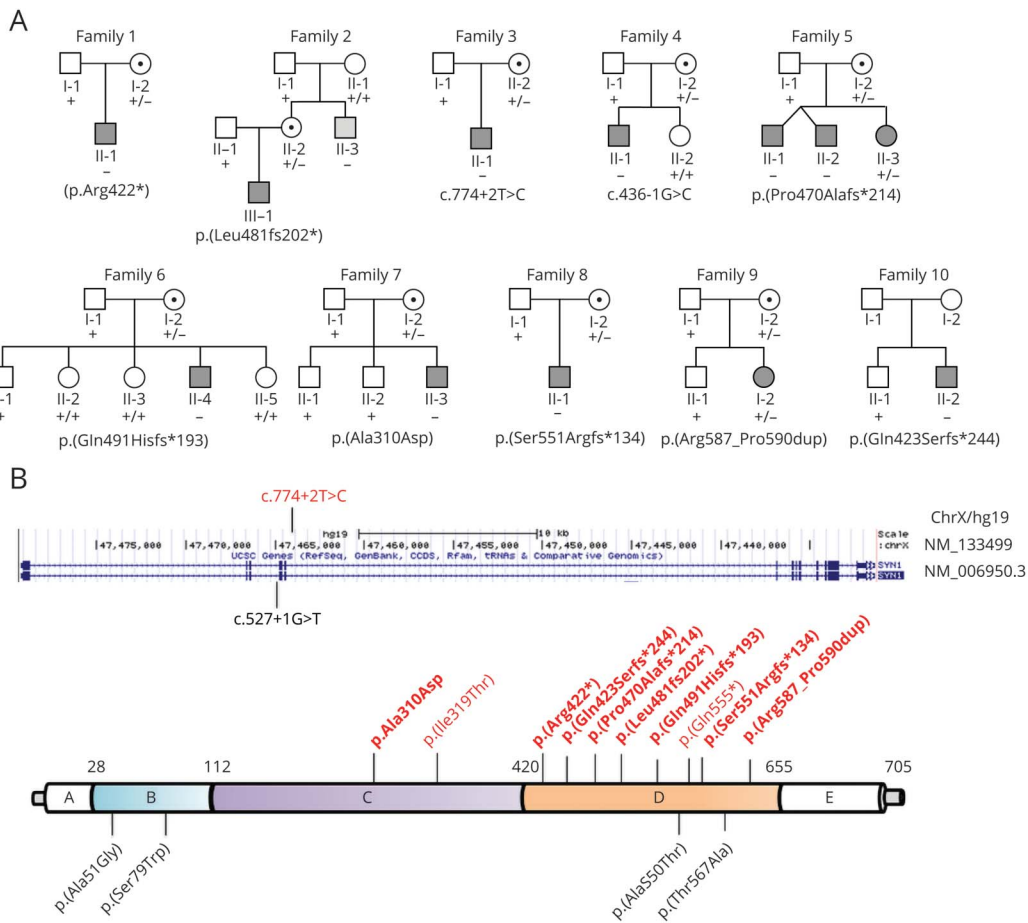
Additional anonymized data that support the findings of this study are available from the corresponding author (P.S.) on reasonable request. Not all of the data are publicly available because they contain information that could compromise children’s privacy and family consent.

## 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

**Figure 1** Pedigrees and *SYN1* Mutations of Affected Patients



(A) Pedigree of the 10 families showing affected members with bathing epilepsy (BE) (shaded in gray) and healthy female carriers (indicated with a central dot); the uncle of family 2 (II:3) with unprovoked seizure is shown in light gray. (B) Nonsense, frameshift, and missense variants in *SYN1* (NM\_006950.3) are depicted along with the Synapsin-1 structure (bottom; protein domains: A; B, linker; C, actin-binding and synaptic-vesicle binding; D, Pro-rich linker; E), and splicing variants are displayed along the genomic locus (top). *SYN1* variants related to BE are in red, and those linked to other clinical presentations than BE are in black. Variants identified in our cohort with BE are in bold.

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 1–5). 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.

**Table 1** Genetic and Phenotypic Features of Subjects With *SYN1* Variants and BE

	<b>Family 1</b>	<b>Family 2</b>	<b>Family 3</b>	<b>Family 4</b>	<b>Family 5</b>			<b>Family 6</b>	<b>Family 7</b>	<b>Family 8</b>	<b>Family 9</b>	<b>Family 10</b>
	<b>II:1</b>	<b>II:1</b>	<b>II:1</b>	<b>II:2</b>	<b>II:1</b>	<b>II:2</b>	<b>II:3</b>	<b>II:4</b>	<b>II:3</b>	<b>II:1</b>	<b>II:2</b>	<b>IV:2</b>
<b>Age, sex</b>	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	5 y F	47 y M
<b><i>SYN1</i> variant (NM_006950.3)</b>	c.1264C>T p.(Arg422*)	c.1439dupC p.(Leu481fs202*)	c.774+2T>C	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.1760_1771dup p.(Arg587_Pro590dup)	c.1266delA p.(Gln423Serfs*244)
<b>Detection analysis/ Segregation</b>	Sanger sequencing De novo	Sanger sequencing Maternal	Sanger sequencing Maternal	Sanger sequencing Maternal	WES Maternal			Gene panel Maternal	Sanger sequencing Maternal	Sanger sequencing Maternal	WES Maternal	Gene panel Presumed maternal
<b>FH of BA</b>	No	Yes, maternal uncle	No	No	Yes, sister	Yes, sister	Yes, brothers	No	No	No	Yes, maternal aunt	Yes, 7 maternal male relatives
<b>Development</b>	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, ADHD	Mild GDD, speech delay, autistic features	GDD, moderate ID, ASD, ADHD	Normal	GDD, mild ID, ASD, motor stereotypies ADHD	GDD, severe ID, ADHD	Mild GDD, speech delay, mild ID, autistic traits
<b>Age at RE onset</b>	5 y	2 y	7 y	8 y	22 mo	14 mo	2 y	4 y 7mo	1 y 3mo	8 mo	8 mo	15 y
<b>RE onset</b>	After showering, rubbing with towel, watching his sister having a shower	During or after bathing	During or after showering, rubbing with towel	During showering (pouring water over the head)	During bathing	During bathing	During bathing	After bathing/ showering, haircutting, fingernail clipping, watching someone while bathing, idea of bathing	During or after bathing, hair washing	After bathing, showering, fingernail clipping	During or after bathing/ showering	During immersion of the feet in water and during febrile events illnesses.
<b>Features</b>	Impaired awareness, pallor, cyanosis, oral automatisms, hypotonia	Impaired awareness, lip cyanosis, buccal automatisms, hypertonus	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)
<b>Seizure frequency at the onset</b>	Weekly	Monthly	1–2/wk	Weekly	Weekly	Weekly	Weekly	2–8/mo	1–2/wk	2–3/wk	2–3/wk	1–2/wk

Continued

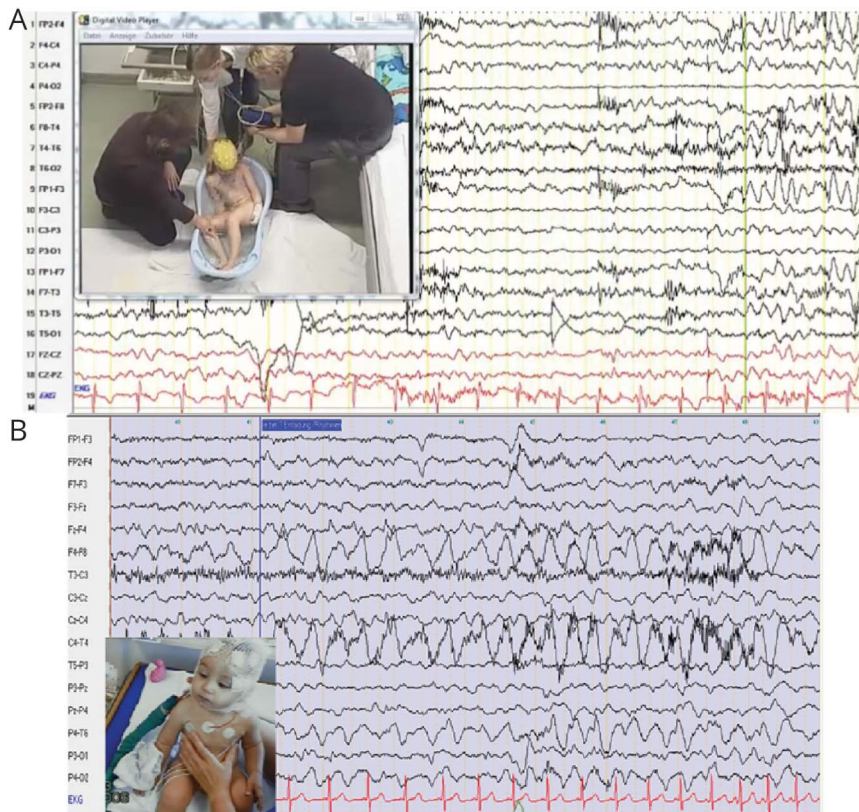
**Table 1** Genetic and Phenotypic Features of Subjects With *SYN1* Variants and BE (continued)

	Family 1	Family 2	Family 3	Family 4	Family 5			Family 6	Family 7	Family 8	Family 9	Family 10
	II:1	II:1	II:1	II:2	II:1	II:2	II:3	II:4	II:3	II:1	II:2	IV:2
<b>Febrile seizure</b>	Yes (4 y 9 mo)	No	No	No	No	No	No	No	Yes (3 y)	No	No	Yes, between 9 and 18 mo
<b>Other seizures</b>	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 5 y	Nocturnal autonomic seizures, 1 y 3 mo	Nocturnal autonomic seizures, TCS SE, 7 y	Infantile spasms, 8 mo; TCS with automatism, 2 y; atonic atypical absence seizures	Focal to bilateral TCS; nocturnal TCS in cluster
<b>EEG interictal</b>	R temporal, L anterior temporal	L frontotemporal	R central, temporal	Normal	Bilateral temporal	Bilateral temporal	Theta activity over the right temporal regions	Bilateral centrottemporal	Normal	R and L temporal	Bursts of slow spike-wave	Twice, normal in adulthood
<b>Ictal</b>	NA	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
<b>ASMs</b>	CLB, VPA	CLB, VGB, CBZ, CLB	CLB	NA	VPA	VPA	VPA	VPA, STM, LTG	CBZ	OXC, STM, VPA, LTG	LTG, VPA, VGB, LAC, LEV, BRV, ZNS, steroids, KD, CBL, RUF	CBZ, LTG, VPA
<b>Response to medications</b>	Decreased seizures frequency	Partial response	Decreased seizures frequency	NA	Poor response	Poor response	Seizure-free	No	Seizure-free, avoidance of warm water	Seizure-free	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.



**Figure 2** Ictal EEG in 2 Patients With *SYN1*



(A) Ictal-video EEG (after bathing) of participant II:4 of family 6 showing the onset of seizure with initial theta high-voltage polymorphic activity over the frontal-temporal region. (B) Ictal-video EEG (after bathing) of participant II:3 of family 7 showing high-voltage polymorphic theta activity over the right frontal-temporal area.

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.<sup>10</sup>

### 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,<sup>18</sup> 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.(Gln423Serfs\*244)] 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.<sup>15</sup> However, since the first report of 7 individuals belonging to the same large French-Canadian family carrying the truncating variant p.(Gln555\*),<sup>17</sup> only 2 additional individuals harboring distinct nonsense p.(Arg422\*)<sup>18</sup> and missense p.(Ile319Thr) variants<sup>19</sup> 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,<sup>18</sup> 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<sup>17</sup> 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 showering 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.<sup>9,17</sup> 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.<sup>22</sup> 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.<sup>22,23</sup> Although the exact pathophysiology of *SYN1*-related BE is currently unknown, the ictal SPECT findings in some individuals have suggested insular cortex involvement.<sup>17</sup> Indeed, the insula is a key integrative multisensory area, well connected with the temporal lobe<sup>24</sup> and potentially able to generate motor and autonomic symptoms, like those observed in BE cases, if functionally perturbed by genetic mutations.<sup>17</sup> 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.<sup>17</sup>

REs represent a spectrum of conditions characterized by broad clinical and genetic heterogeneity and several overlapping features.<sup>1,6</sup> Apart from *SYN1*, a few additional RE-related genes have been reported, including *SYNGAP1* in individuals with chewing reflex,<sup>25,26</sup> *CDKLS*-related disorders exhibiting diaper change reflex,<sup>27</sup> *SCN1A* in somatosensory reflex seizures,<sup>28</sup> and *CHD2* in photosensitive seizures.<sup>5</sup> 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.<sup>20</sup> Thus, to specifically address this issue, we screened a cohort of cases



showing HWE and found no evidence of pathogenic variants in *SYNI*.

HWE, largely reported in southern India, is induced by bathing with hot water usually >37°C.<sup>29</sup> Seizures often occur when individuals are seated and hot water is poured from a washtub or basin over their heads.<sup>10,29</sup> 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 ≈20% to 40% of individuals with HWE may develop spontaneous seizures,<sup>8</sup> 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.<sup>30,31</sup> SPECT studies have demonstrated ictal hypermetabolic uptake in the medial temporal structures and hypothalamus.<sup>32</sup> 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.<sup>33,34</sup>

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 HWE<sup>33</sup> and the report of a few individuals with BE who also experienced seizure precipitated by rubbing the face with a wet cloth or nail clipping<sup>17</sup> 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 *SYNI* 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 *SYNI*-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.<sup>35</sup> 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 *SYNI*-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.

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## Appendix Authors

Name	Location	Contribution
<b>Andrea Accogli, MD</b>	Istituto Giannina Gaslini, Genoa, Italy	Data acquisition, drafting the initial manuscript, analysis and interpretation of data, and finalizing manuscript with all authors' input
<b>Gert Wiegand, MD</b>	University Medical Centre Schleswig-Holstein, Kiel, Germany	Data acquisition, analysis and interpretation of data, drafting and finalizing the manuscript
<b>Marcello Scala, MD</b>	Istituto Giannina Gaslini, Genoa, Italy	Drafting and final revision of the manuscript
<b>Caterina Cermignara, MD</b>	Tor Vergata University, Roma, Italy	Patient recruitment, data analysis, and final revision of the manuscript

## Appendix (continued)

Name	Location	Contribution
<b>Michele Iacomino, PhD</b>	Istituto Giannina Gaslini, Genoa, Italy	Genetic analysis, data analysis
<b>Antonella Riva, MD</b>	Istituto Giannina Gaslini, Genoa, Italy	Patient recruitment, clinical assessment, final revision of the manuscript
<b>Barbara Carlini, MSc</b>	Istituto Giannina Gaslini, Genoa, Italy	Genetic analysis
<b>Letizia Camerota, MD</b>	University of L'Aquila, Italy	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Vincenzo Belcastro, MD</b>	Neurology Unit, Maggiore Hospital, ASST-Lodi, Lodi, Italy	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Paolo Prontera, MD, PhD</b>	Medical Genetics Unit, "S. Maria della Misericordia" Hospital, Perugia, Italy	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Alberto Fernández-Jaén, MD, PhD</b>	Hospital Universitario Quirónsalud and Universidad Europea de Madrid, Spain	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Nerses Bebek, MD, PhD</b>	Istanbul University Istanbul Faculty of Medicine Department of Neurology, Turkey	Recruitment of patients with HWE
<b>Paolo Scudieri, PhD</b>	Istituto Giannina Gaslini, Genoa, Italy	Genetic testing
<b>Simona Baldassari, PhD</b>	Istituto Giannina Gaslini, Genoa, Italy	Genetic testing
<b>Vincenzo Salpietro, MD</b>	Istituto Giannina Gaslini, Genoa, Italy	Patient evaluation, clinical assessment, and final revision
<b>Giuseppe Novelli, PhD</b>	Tor Vergata University of Rome, Italy	Genetic testing
<b>Chiara De Luca, MD</b>	Human Genetics, Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Celina von Stülpnagel, MD</b>	Department of Pediatrics, University Hospital Munich, Germany	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Felicitas Kluger, MD</b>	Epilepsy Center for Children and Adolescents, Vogtareuth, Germany	Drafting and revision of the manuscript
<b>Gerhard Josef Kluger, MD</b>	Epilepsy Center for Children and Adolescents, Vogtareuth, Germany	Patient recruitment, clinical assessment, and final revision of the manuscript
<b>Gabriele Christine Wohlrab, MD</b>	Department of Neuropediatrics, University Children's Hospital Zurich, Switzerland	Patient recruitment, evaluation, and final revision of the manuscript
<b>Georgia Ramantani, MD</b>	Department of Neuropediatrics, University Children's Hospital Zurich, Switzerland	Patient recruitment, evaluation, and final revision of the manuscript

## Appendix (continued)

Name	Location	Contribution
<b>David Lewis-Smith, MClInRes, MRCP</b>	Translational and Clinical Research Institute, Newcastle University, Newcastle Upon Tyne, UK	Patient recruitment, evaluation, and final revision of the manuscript
<b>Rhys H. Thomas, PhD, FRCP</b>	Translational and Clinical Research Institute, Newcastle University, Newcastle Upon Tyne, UK	Patient recruitment, evaluation, and final revision of the manuscript
<b>Ming Lai, MBBS</b>	Translational and Clinical Research Institute, Newcastle University, Newcastle Upon Tyne, UK	Patient recruitment, evaluation, and final revision of the manuscript
<b>Alberto Verrotti, MD, PhD</b>	Department of Pediatrics, University of L'Aquila, Italy	Patient recruitment, evaluation, and final revision of the manuscript
<b>Salvatore Striano, MD</b>	Epilepsy Center, Federico II University, Napoli, Italy	Patient recruitment, evaluation, and final revision of the manuscript
<b>Christel Depienne, PhD</b>	Institut für Humangenetik, Universitätsklinikum Essen, University Duisburg-Essen, 45147 Essen, Germany	Patient recruitment, evaluation, and final revision of the manuscript
<b>Carlo Minetti, MD, PhD</b>	Istituto Giannina Gaslini, Genoa, Italy	Patient recruitment, evaluation, and final revision of the manuscript
<b>Fabio Benfenati, MD, PhD</b>	Center for Synaptic Neuroscience and Technology, Istituto Italiano di Tecnologia, Genoa, Italy	Critical revision and final revision of the manuscript
<b>Francesco Brancati, MD, PhD</b>	Human Genetics, Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy	Patient recruitment, evaluation of genetic testing, final revision of the manuscript
<b>Federico Zara, PhD</b>	Istituto Giannina Gaslini, Genoa, Italy	Principal investigator, coordinator of the genetic testing, revision of final the manuscript
<b>Pasquale Striano, MD, PhD</b>	Istituto Giannina Gaslini, Genoa, Italy	Principal investigator, lead of the design and conceptualization of the study, critical revision of the manuscript

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