Identification of a possible pathogenic link between congenital long QT syndrome and epilepsy

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ABSTRACT

Background: Long QT syndrome (LQTS) typically presents with syncope, seizures, or sudden death. Patients with LQTS have been misdiagnosed with a seizure disorder or epilepsy and treated with antiepileptic drug (AED) medication. The gene, *KCNH2*, responsible for type 2 LQTS (LQT2), was cloned originally from the hippocampus and encodes a potassium channel active in hippocampal astrocytes. We sought to test the hypothesis that a "seizure phenotype" was ascribed more commonly to patients with LQT2.

Methods: Charts were reviewed for 343 consecutive, unrelated patients (232 females, average age at diagnosis 27 ± 18 years, QTc 471 ± 57 msec) clinically evaluated and genetically tested for LQTS from 1998 to 2006 at two large LQTS referral centers. A positive seizure phenotype was defined as the presence of either a personal or family history of seizures or history of AED therapy.

Results: A seizure phenotype was recorded in 98/343 (29%) probands. A seizure phenotype was more common in LQT2 (36/77, 47%) than LQT1 (16/72, 22%, $p < 0.002$) and LQT3 (7/28, 25%, $p < 0.05$, NS). LQT1 and LQT3 combined cohorts did not differ significantly from expected, background rates of a seizure phenotype. A personal history of seizures was more common in LQT2 (30/77, 39%) than all other subtypes of LQTS (11/106, 10%, $p < 0.001$).

Conclusions: A diagnostic consideration of epilepsy and treatment with antiepileptic drug medications was more common in patients with LQT2. Like noncardiac organ phenotypes observed in other LQTS-susceptibility genes such as *KCNQ1*/deafness and *SCN5A*/gastrointestinal symptoms, this novel LQT2-epilepsy association raises the possibility that LQT2-causing perturbations in the *KCNH2*-encoded potassium channel may confer susceptibility for recurrent seizure activity. **Neurology® 2009;72:224–231**

GLOSSARY

AED = antiepileptic drug; **LQT1** = type 1 LQTS; **LQT2** = type 2 LQTS; **LQTS** = long QT syndrome; **TdP** = torsades de pointes.

Congenital long QT syndrome (LQTS) was first described as Jervell and Lange-Nielsen syndrome and Romano Ward syndrome in the late 1950s and early 1960s.[1-3] LQTS is now understood as a collection of genetically distinct arrhythmogenic disorders resulting from genetic mutations in cardiac potassium and sodium ion channels, thus termed cardiac channelopathies.[4] Recent investigations have shown that mutations in non-channel proteins can also cause LQTS.[5,6] The trademark event for the patient with symptomatic LQTS is the potentially lethal ventricular dysrhythmia known as torsades de pointes (TdP).[7] TdP can precipitate syncope, seizures, or sudden death, depending on whether the heart rhythm spontane-

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ously reverts to normal rhythm or if the patient is defibrillated back to normal rhythm before death occurs.[8,9]

LQTS affects approximately 1 in 2,500 persons and patients with LQTS are often diagnosed with a seizure disorder, being fainters, or having "spells."[10] Numerous LQTS genotype-specific arrhythmogenic triggers have been identified.[11,12] For example, swimming is relatively gene-specific for type 1 LQTS (LQT1)[13,14] while events that occur in women during the postpartum period, as well as those triggered by auditory stimuli, often indicate the presence of type 2 LQTS (LQT2).[12,15-18] The onset of TdP has been shown recently to be gene-specific as well, with LQT2 patients preferentially having pauses in cardiac rhythm prior to the onset of TdP.[19] Besides the long appreciated sensorineural hearing loss observed in patients with bi-allelic *KCNQ1* mutations (i.e., Jervell and Lange-Nielsen syndrome),[5] the search for noncardiac phenotypic expression involving other organs continues. For example, patients with LQT3-causing *SCN5A* mutations have been demonstrated to have an increased prevalence of gastrointestinal symptoms.[20]

In 1995, loss-of-function mutations in the 1,159 amino acid-containing alpha subunit of the rapidly activating delayed rectifying potassium channel, I_{Kr}, encoded by the *human ether a go-go related gene, HERG,* were discovered as the cause for LQT2.[21] In addition, the *Drosophila* homolog of the *HERG* gene was found to be encoded by the aptly named *seizure* locus. Mutations in the *seizure* locus caused temperature-induced hyperactivity followed by paralysis in *Drosophila*.[22] Notably, the *HERG* gene, now annotated as *KCNH2*, was discovered originally in a hippocampal cDNA library in 1994, although murine *ERG* is expressed in other regions of the brain as well.[23] Further studies reported that hippocampal expression of the ERG family of potassium channels is distributed preferentially to hippocampal astrocytes[24] that may regulate neuronal excitability.[24-27]

Considering that the LQT2-associated HERG potassium channel is present and active in significant quantity in glial cells, and recognizing that blockage of potassium homeostasis in glial cells can be epileptogenic,[24-26] it is tempting to speculate that patients with LQTS, particularly type 2 LQTS, may in fact exhibit neurally mediated seizures or epilepsy rather than simply a ventricular arrhythmia with subsequent collapse and seizure activity (i.e., torsadogenic seizures). Accordingly, we set out to test the hypothesis that either a prior personal or family history of seizure activity or treatment with antiepileptic drug (AED) medication were more common among patients with LQT2.

METHODS

Chart review. In this IRB-approved study, the medical records were reviewed for all unrelated patients (n = 343) clinically evaluated and genetically tested for LQTS between 1998 and 2006 at two LQTS referral centers: 1) Mayo Clinic's Long QT Syndrome Clinic in Rochester, MN (n = 208) and 2) the Academic Medical Center, Amsterdam, The Netherlands (n = 135). The reviewers (J.N.J., N.H.) were blinded at all times to the patients' genotypes.

Classifications of patients were given based on genotype by a third author (C.M.H.) independent of the reviewers. Patients were classified as genotype positive LQTS if they had a clinically relevant genetic mutation in one of the known LQTS-susceptibility genes. Patients were classified as genotype negative LQTS if they had a clinical diagnosis of LQTS given by a physician specializing in LQTS (M.J.A., A.A.M.W.), but in whom genetic testing of the known LQTS-susceptibility genes was negative. A classification of normal was given if the patient had a negative genetic test as well as a negative clinical history for LQTS as determined by a physician specializing in LQTS (M.J.A., A.A.M.W.).

A positive "seizure phenotype" was defined as the presence of either a personal or family history of seizures or epilepsy or a history of AED therapy. A family history of seizures was considered positive if the patient could name the affected family member, and if the family member shared genetic material with the proband. Family members with a history of seizures but who had married into the family were excluded. Vague histories of seizures in distant family members not clearly known by the proband and their immediate family were excluded. Only unrelated patients were reviewed to prevent the presence of a few large families from skewing the family history data. A patient was considered to have a positive treatment history if they had been placed on an AED medication for greater than 1 day, and if the medical treatment was specifically prescribed for a presumed seizure disorder. AED treatment for nonepileptic conditions (e.g., chronic pain) was not included. Given that the current standard of care for the evaluation of LQTS does not include an EEG, documented EEG evidence of epileptiform activity was not a requirement for inclusion in this study.

We attempted to account for and exclude all acquired causes of seizures in the cohorts. Patients with a history of having a single seizure with documented fever were excluded. Also, patients with a history of seizures within months following a traumatic head injury (or patient's family members with a similar history) were excluded. All other seizure histories were classified as a positive seizure phenotype.

Genetic testing. Patients in both the Mayo Clinic and Amsterdam cohorts had genetic testing performed using denaturing high performance liquid chromatography and direct DNA sequencing. For the Mayo cohort, comprehensive genetic testing

Table 1 Demographic and genotype data

Cohort	Combined cohort	Mayo cohort	Amsterdam cohort	p Value
No. of patients	343	208	135	—
Age, y, mean ± SD	27 ± 18	24 ± 15	32 ± 22	0.001*
QTc, ms, mean ± SD	471 ± 57	467 ± 50	476 ± 65	0.15
% Female	68	68	67	0.94
% With positive "seizure phenotype"	29	24	36	0.023*
% With personal seizure history	20	13	30	<0.001*
% With seizure treatment history	7	4	13	0.004*
Total genotype positive patients	183 (53%)	105 (50%)	78 (58%)	0.23
No. LQT1 (KCNQ1)	72	48	24	0.30
No. LQT2 (KCNH2)	77	39	38	0.06
No. LQT3 (SCN5A)	28	13	15	0.16
No. LQT5 (KCNE1)	4	4	0	0.16
No. LQT6 (KCNE2)	1	0	1	0.39
No. LQT7 (KCNJ2)	1	1	0	1
Total genotype negative patients	160	103	57	0.27
Genotype (–) phenotype (+)	70	31	39	0.002*
Genotype (–) phenotype (–)	90	72	18	<0.001*

Demographic data and genotype/phenotype classification of proband patients presenting to Mayo Clinic, Rochester, MN, and Academic Medical Centre, Amsterdam. p Values refer to the differences between the individual Mayo and Amsterdam cohorts.
*$p < 0.05$.

for additional mutations in the five most common LQTS-susceptibility genes was performed routinely even after the first mutation was found, given that multiple mutations occur at a frequency of 5–10%. For the Amsterdam cohort, further genetic testing after first mutation identification was per protocol and was continued only if there was a severely prolonged QT interval or if the patient was symptomatic. The vast majority of the patients in the Amsterdam cohort of this study, however, were symptomatic, and thus had comprehensive assessment of at least *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3), which accounts for approximately 75% of all LQTS and over 95% of the patients with genetically identifiable LQT1-12 genotypes.

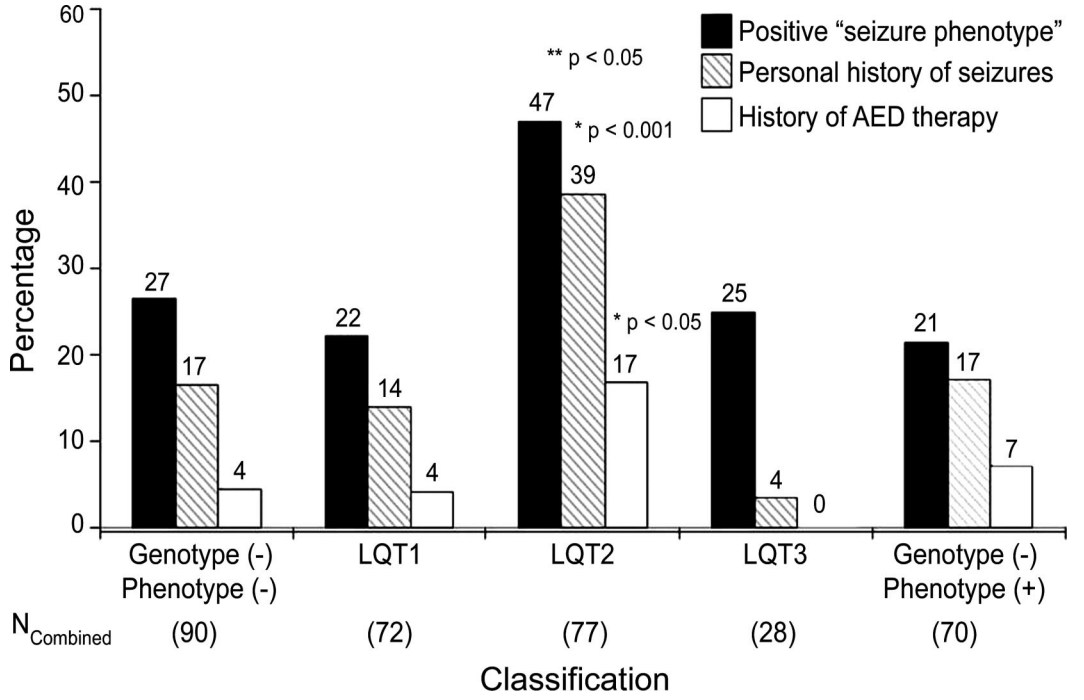
Statistical analysis. Statistical analyses were performed with the assistance of the Mayo Clinic CTSA Service Center, Rochester, MN. All continuous variables were reported as the mean ± SD. Proportions were analyzed and compared using a two-tailed Fisher exact test. Means were analyzed using the independent groups *t* test for means. QTc values were measured manually and calculated using the standard Bazett formula.[28] A p value < 0.05 was considered to be significant.

RESULTS Table 1 summarizes the demographics for the composite cohort and the individual Mayo Clinic and Amsterdam cohorts. Demographically, age was the sole significant difference between the two cohorts, with the Mayo cohort having a younger patient population (24 ± 15 years) than the Amsterdam cohort (32 ± 22 years, $p = 0.001$). Otherwise, there were no other significant differences found between the cohorts in terms of proportion of each genotype, QTc at diagnosis, or percent of patients with positive or negative genotypes.

Overall, a positive seizure phenotype was recorded in 98/343 (29%) patients including 24% of the Mayo Clinic cohort and 36% of the Amsterdam cohort (table 1, $p = 0.023$). Twenty percent of the probands either had a personal history of seizures or were diagnosed clinically with epilepsy prior to the rendering of genotype proven LQTS. A personal seizure history was more common among the 135 unrelated cases in the Amsterdam cohort (30%) compared to the 208 unrelated cases in the Mayo Clinic cohort (13%, $p < 0.001$). In addition, 7% of the patients had received antiepileptic pharmacotherapy including 13% of the Amsterdam cohort compared to 4% of the Mayo Clinic cohort ($p = 0.004$).

Among the 90 patients ultimately dismissed as normal (genotype negative/LQTS phenotype negative), 27% had a positive seizure phenotype, 17% had been diagnosed as having seizures, and 4% had been treated with AED medications (figure). In comparison, unrelated patients with genetically or clinically diagnosed LQTS had a similar prevalence of a positive seizure phenotype overall (31%, p = NS). However, subset analysis revealed that a positive seizure phenotype, a personal history of seizures, and a personal history of antiepileptic therapy was more common among patients with LQT2 (figure). In fact, a pos-

Figure Prevalence of "seizure phenotype" in long QT syndrome subtypes



Percentage of patients from the combined cohort for each genotypic classification having a positive seizure phenotype (black bar), personal history of seizures (diagonal line), or history of treatment for seizures with antiepileptic drugs (AEDs, white bar). Not shown are patients with LQT5, LQT6, and LQT7 (n = 6), none of whom had a positive seizure phenotype. *Significance value of combined cohort of LQT2 patients compared to other long QT genotypes. **Significance value of combined cohort of LQT2 patients compared to the other LQTS genotypes (i.e. LQT1 and LQT3) and the genotype negative background rates. When compared to LQT3, LQT2 is more common (47% vs 25%) but did not achieve significance (p = 0.07).

itive seizure phenotype was recorded in nearly half (36/77) of the patients with LQT2 compared to 16/72 (22%, $p < 0.002$) with LQT1, 7/28 (25%, NS) with LQT3, and 15/70 (21%, $p < 0.002$) with genotype negative/phenotype positive LQTS. Analysis of the Mayo Clinic and Amsterdam cohorts separately indicate this increased prevalence of positive seizure phenotype in LQT2, 36% in the Mayo Clinic cohort and 58% in the Amsterdam cohort.

Similarly, patients with LQT2 were far more likely to have a personal history of seizures or a preceding diagnosis of epilepsy (39%) compared to either the genotype negative/phenotype negative patients (17%) or the other subtypes of LQTS (11/106, 10%, $p < 0.001$, figure). This increased prevalence of personal seizures in LQT2 was evident in both cohorts independently: 26% vs 6% in the Mayo Clinic cohort ($p < 0.008$) and 53% vs 18% in the Amsterdam cohort ($p < 0.001$). A previous diagnosis of seizure disorder was more common among LQT2 patients seen in Amsterdam compared to the LQT2 patients evaluated at the Mayo Clinic ($p < 0.02$). Among the patients with LQT2 and a personal history of seizures (n = 30), 13 (17% of all LQT2 patients) had been treated with antiepileptic pharmacotherapy (9/20 from Amsterdam and 4/10 from Mayo Clinic) compared to only 12/266 (4.5%) non-LQT2 patients ($p < 0.001$) including 4% with LQT1, 0% with LQT3, 7% with genotype negative/phenotype positive LQTS, and 4% of patients that lacked both genetic and clinical evidence for a diagnosis of LQTS (figure).

A summary of the mutations noted in patients who have both LQT2 and a positive seizure phenotype is shown in table 2. There were no associations seen between patients with a personal or family history of seizures and the location of the mutation in the potassium channel.

DISCUSSION It is well known that the most common symptomatic triad stemming from TdP (the trademark dysrhythmia of LQTS) is syncope, seizures, or sudden death.[7] Seizures have been viewed as the sequelae of prolonged cerebral hypoperfusion secondary to the cardiac dysrhythmia (i.e., torsadogenic seizures). Because these patients may be witnessed having an apparent generalized seizure, it is not uncommon for patients with LQTS to be misdiagnosed with epilepsy and treated with AED medication.[7,29]

Here, we demonstrate that among two independent cohorts of unrelated patients evaluated clinically and genotyped for LQTS, a seizure phenotype was far more commonly ascribed to patients with LQT2

Table 2 Mutations in patients with LQT2 and a positive "seizure phenotype"

Patient no.	Institution	History type	Exon	Nucleotide change	Coding effect	Location
1	Mayo	Personal	2	89 T>C	I30T	N-term
2	AMC	Personal	2	191 G>A	C64Y	N-term
3	Mayo	Personal	2	Del221-251	R73fs/31	N-term
4	AMC	Family	2	296 A>G	Y99S	N-term
5	AMC	Personal	2	296 A>C	Y99S	N-term
6	Mayo	Personal	4	526 C>T	R176W	N-term
7	AMC	Personal	4	Del578-582	A193fsX329	N-term
8	AMC	Personal	4	722 C>T	P241L	N-term
9	AMC	Personal	4	754delC	R252G	N-term
10	Mayo	Personal	4	916 G>T	G306W	N-term
11	Mayo	Personal	5	1096 C>T	R366X	N-term
12	Mayo	Family	5	1128 G>A	Q376sp	N-term
13	Mayo	Personal	6	1366 G>T	D456Y	S2
14	AMC	Personal	6	1501 G>C	D501H	S3
15	AMC	Personal	7	1600 C>T	R534C	S4
16	AMC	Personal	7	1674 C>G	A558P	S5
17	AMC	Personal	6/7	1129-2543_1678 Dup3682	I560fs/2	S5
18	AMC	Personal	7	1714 G>A	G572S	S5-Pore
19	AMC	Personal	7	1744 C>T	R582C	S5-Pore
20	AMC	Personal	7	1744 C>T	R582C	S5-Pore
21	Mayo	Personal	7	1838 C>T	T613M	Pore
22	AMC	Personal	7	1838 C>T	T613M	Pore
23	Mayo	Personal	7	1886 A>T	N629I	Pore
24	Mayo	Family	7	1898 A>G	N633S	Pore-S6
25	Mayo	Family	7	1918 T>G	F640V	S6
26	AMC	Personal	7	1920 C>A	F640L	S6
27	AMC	Personal	7	del1926-1934	del I642-V644	S6
28	AMC	Personal	7	1933 A>C	M645L	S6
29	AMC	Family	7	1945 T>C	S649P	S6
30	AMC	Personal	8	del2027-2028	Q676fsX721	S6-cNBD
31	AMC	Personal	8	2062 C>T	E698X	S6-cNBD
32	AMC	Personal	11	2616delC	P872fs877	C-term
33	Mayo	Personal	11	2626 G>T	E876X	C-term
34	Mayo	Family	12	2705delC	Q901fs/71	C-term
35	AMC	Personal	12	2775delG	G925fs/47	C-term
36	Mayo	Personal	13	3108insG	G1036fs/82X	C-term

Mutation data on the 36 LQT2 patients with a positive seizure phenotype presenting to either the Mayo Clinic, Rochester, MN, or the Academic Medical Centre (AMC), Amsterdam. Thirty of these patients had a personal history of seizures while six had a family history.

compared to either background rates or to patients with LQT1. A positive seizure phenotype was also more common in LQT2 compared to LQT3, but due to low total numbers of LQT3 patients, significance was not achieved. It is important to note that, while 39% of LQT2 patients had been labeled as having seizures, only a single patient with LQT3 had a personal history of seizures ($p < 0.001$).

Nearly half of the patients with LQT2 were classified as having either a personal or family history of seizures or history of AED therapy. In fact, patients with LQT2 were three to four times more likely to have been labeled with a personal history of seizures or formally given a diagnosis of epilepsy compared to patients without LQT2. In addition, nearly one out of five patients with LQT2 had been treated with

antiepileptic pharmacotherapy compared to less than 1 out of 20 patients with LQT1 and none of the 28 patients with LQT3. Just like previous phenotype-genotype associations that identified auditory triggers as a relatively LQT2-specific arrhythmogenic trigger[18] and the postpartum period as a relatively LQT2-specific temporal period for increased risk among women,[17,30] seizures/epilepsy can now be added as far more suggestive of LQT2 genotype status than any other genotype.

KCNH2 was isolated originally from a hippocampal cDNA library.[23] It is important to note that both the SCNA sodium channel family and KCNQ family of potassium channels have also been cloned in neuronal tissue.[31-34] Indeed, it has been speculated that patients with SCN5A mutations could have an increased incidence of seizures.[35] Our data only support an increased risk of seizure diagnosis in LQT2 compared to background. Neither LQT1 (KCNQ1) nor LQT3 (SCN5A) patients had a significantly greater seizure diagnosis frequency when compared to normal patients. Thus, even though there is similar neuronal expression of the two other main LQTS-susceptibility genes, LQT2 appears to be the only subtype commonly associated with a clinical expression of seizures.

Intriguingly, *KCNH2*-encoded potassium channels are instrumental in potassium homeostasis in hippocampal glia.[24] Pharmacologic studies have also shown a relationship between preventing voltage-dependent potassium buffering in astrocytes and the development of epileptiform activity in the hippocampus.[27,36] Voltage dependent buffering refers to the neurologic process whereby glia control the potassium concentration in the extraneuronal space in order to maintain normal neuronal conduction of action potentials.[37] There has to be a constant extraneuronal potassium concentration in order for the action potential to effectively start and stop as needed. If this is perturbed, there is enhanced susceptibility for epileptic activity.[36] Interestingly, blocking ERG potassium channels in astrocytes changes potassium concentrations extraneuronally,[24] and such changes in potassium concentrations extraneuronally have been shown to be epileptogenic.[36]

Mechanistically, it is therefore conceivable that patients with LQT2 may have a decreased seizure threshold secondary to cerebral hypoperfusion stemming from a LQT2-precipitated cardiac dysrhythmia of TdP due in part to the perturbation in the neuronal *KCNH2*-encoded potassium channels that reside in the hippocampus. Alternatively, it is tempting to speculate that perhaps some of the "cardiac events" in patients with LQT2 are actually neurally mediated seizures secondary to the defect in the hippocampal potassium channels encoded by *KCNH2*. If patients with LQT2 have a tendency for neurally mediated seizures, then *KCNH2* may represent a novel candidate gene for certain types of epilepsy, particularly temporal lobe epilepsy.

It should be noted that *ERG* potassium channel-encoding genes have been shown to be expressed in numerous locations in mouse brain tissue, not limited to the hippocampus.[38] Thus, epileptiform involvement of *HERG* mutations in humans may not only be limited to the hippocampus or temporal lobe. An alternate plausible explanation is that seizure activity could occur secondary to hypoxic-ischemic injury to the hippocampus from unrecognized arrhythmias. This theory would not however explain the specific predominance of seizure history in LQT2 patients compared to other LQTS patients.

Unfortunately, erroneous treatment of LQTS patients with AEDs may in fact be harmful to the patient. Overall, 7% of patients in this study were treated with AED medications. Prior whole cell-patch clamp studies demonstrated that phenobarbital and phenytoin could block HERG-related currents potentially conferring susceptibility to drug-induced TdP, particularly in predisposed patients.[39] While this is intriguing, it is also important to note that several antiepileptic medications, including phenytoin, are in part sodium channel blockers and are potentially anti-arrhythmic. In fact, decades ago, phenytoin was commonly used pharmacotherapy for patients with LQTS. Clearly, the results from this LQT2-seizure genotype/phenotype analysis call for further cardiac and neurologic pharmacology interaction studies.

Due to the retrospective study design, there exists the potential for reporting bias in the data collection process. However, the LQTS physicians (M.J.A., A.A.M.W.) solicited data regarding personal or family history of seizures or history of AED therapy uniformly and systematically in their clinical practices, and although not blinded to the patient's genotype, the genotype was generally not established during the initial LQTS consultation. Regardless of the vantage point, a seizure phenotype was more common among patients with LQT2. However, statistical correction for multiple comparisons was not performed.

In addition, we noted that the prevalence of a seizure phenotype in LQT2 was statistically greater among LQT2 patients evaluated in Amsterdam compared to those evaluated at the Mayo Clinic. It is possible that there could be an additional environmental/ethnic contribution. Considering that the patients in the Amsterdam cohort were significantly older on average than those in the Mayo cohort, it is also possible that the Amsterdam cohort simply had

more life-years to have experienced a personal or family history of seizures. Regardless, the greater frequency of a personal history of seizures or prior diagnosis of epilepsy and prior treatment with AEDs among patients with LQT2 was completely concordant between both LQTS centers.

Due to the acute and unpredictable onset of clinical events in patients with LQTS, EEGs during events were unavailable to the authors. A postictal EEG was not available either. This is not surprising, however, as an EEG is not viewed as standard of care in the clinical evaluation of patients with LQTS. Certainly, functional proof of neuronally mediated seizure activity in LQT2 patients while in normal sinus rhythm would lend credence to one of the postulated mechanisms. As stated previously, those labeled with a seizure phenotype in this study, in the absence of EEG evidence, may simply have expressed seizure activity following their cardiac-mediated syncopal episode. Regardless of the underlying mechanism, however, two independent cohorts have evidenced a proclivity for seizure labeling among patients with mutations in the *KCNH2*-encoded, cardiac/neuronal-expressed potassium channel (LQT2). Just as it is debated whether all patients evaluated for generalized epilepsy should have a screening electrocardiogram, this new genotype–phenotype association will likely prompt a new dialogue as to whether patients with LQTS, particularly LQT2, should have a wake- and sleep-deprived EEG.

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