Low Incidence of Sudden Cardiac Death in a Swedish Y111C Type 1 Long-QT syndrome Population

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Background—A 10% cumulative incidence and a 0.3% per year incidence rate of sudden cardiac death in patients younger than 40 years and without therapy have been reported in type 1 long-QT syndrome. The Y111C-KCNQ1 mutation causes a severe phenotype in vitro, suggesting a high-risk mutation. This study investigated the phenotype among Y111C-KCNQ1 mutation carriers in the Swedish population with a focus on life-threatening cardiac events.

Methods and Results—We identified 80 mutation carriers in 15 index families, segregating the Y111C-KCNQ1 mutation during a national inventory of mutations causing the long-QT syndrome. Twenty-four mutation carriers <40 years experienced syncope (30%). One mutation carrier had an aborted cardiac arrest (1.25%). No case of sudden cardiac death was reported during a mean nonmedicated follow-up of 25±20 years. This corresponds to a low incidence rate of life-threatening cardiac events (0.05%/year versus 0.3%/year, P=0.025). In 8 Y111C families connected by a common ancestor, the natural history of the mutation was assessed by investigating the survival over the age of 40 years for 107 nonmedicated ascertained mutation carriers (n=24) and family members (n=83) born between 1873 and 1968. In total, 4 deaths in individuals younger than 40 years were noted: 1 case of noncardiac death and 3 infant deaths between 1873 and 1915.

Conclusions—The dominant-negative Y111C-KCNQ1 mutation, associated with a severe phenotype in vitro, presents with a low incidence of life-threatening cardiac events in a Swedish population. This finding of discrepancy emphasizes the importance of clinical observations in the risk stratification of long-QT syndrome.

Key Words: death, sudden (if surviving, use heart arrest) ■ genetics ■ ion channels ■ long-QT syndrome ■ survival

A 10% cumulative incidence of aborted cardiac arrest (ACA) or sudden cardiac death (SCD) in patients younger than 40 years has been reported in type 1 long-QT (LQT1) syndrome for mutation carriers who did not receive prophylactic treatment.1 The LQT1 subgroup is heterogeneous, including several hundred different reported mutations in the KCNQ1 gene,2–4 affecting the ion channel (Ks) that conveys the slow rectifier potassium current in the cardiac myocytes.5,6

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Recently, advances in molecular genetics and biophysics have included the in vitro characterization of the effect on ion-channel structure and function by specific mutations or classes of mutations. High-risk mutations have been identified within the LQT1 subgroup.7–11 The Y111C-KCNQ1 (c.332A>G) mutation has previously been described in 1 patient, a 36-year-old woman, who presented with syncope at the age of 3 years.3 She experienced >30 syncopal episodes triggered by emotional or physical stress and had a QT interval, corrected for heart rate, of 520 ms. Electrophysiological studies subsequently demonstrated that the Y111C mutation causes intracellular sequestration of mutated ion channels in the endoplasmic reticulum that renders them inactive.9 Moreover, the mutation exerts a strong dominant-negative effect on the coexpressed wild-type ion channels encoded by the unaffected allele,10 leading to a severely reduced inward potassium current in vitro.9,10

We have observed several Swedish families sharing the same Y111C-KCNQ1 mutation, expressing an apparent benign clinical phenotype. In this study, we describe the phenotype of a Swedish Y111C population with a focus on life-threatening cardiac events.

Methods

Study Design
During a national inventory of LQTS-causing mutations, individuals with clinically suspected LQTS were referred for genetic analysis. Index cases were defined as the first identified mutation carrier in a
family where there was no previous knowledge of LQTS among relatives. Written information regarding the LQTS-causing mutation and the possibility of cascade screening, after genetic counseling, was spread on a voluntary basis by index cases to relatives. For all ascertained mutation carriers (MCs), medical records, ECG recordings, and mutation analysis results were collected. All index cases were subjected to genealogical investigation. In Y111C families connected by a common founder, we noted the date of birth, date of death, and, when appropriate, the cause of death of all nonmedicated family members born between 1873 and 1968 to assess the natural history of the mutation.

**Clinical Data**

Clinical data from medical records were collected. An interview with each family, directing special attention to family history and symptoms, was performed. All participants answered a questionnaire regarding symptoms and personal LQTS history.

Symptomatic LQTS was defined as experience of syncope, ACA, or SCD, not including spells of dizziness, near fainting, or palpitations. The term life-threatening cardiac event encompasses the symptoms ACA and SCD.

**Electrocardiography**

The 12-lead ECGs were recorded at paper speed 50 mm/s and a gain of 1 mV/10 mm. ß-blocker therapy was continued in medicated individuals. When available, ECGs recorded before the initiation of treatment were analyzed. The measurements of QT interval on coded ECGs were performed by 1 observer. QT interval was measured manually in leads II, V5, and V6 in 3 consecutive heartbeats, and the highest average was used. R-R interval was measured as the average of 3 heartbeats preceding each measured QT interval. The QT interval was corrected for heart rate using Bazetts formula (QTc). A QTc >440 ms in men and >460 ms in women was considered prolonged.12 For comparison with other studies, the cutoffs of QTc ≤440 ms and QTc ≥500 ms were used.1,7,8

**Genetic Analysis**

A sample of 2×5 mL whole blood was collected from each patient. Genomic DNA was extracted from peripheral lymphocytes using standard salting out methods. Mutation screening of the KCNQ1 and KCNH2 genes or direct mutation analysis was performed in index cases. DNA was amplified by polymerase chain reaction and subsequently analyzed using denaturing high-performance liquid chromatography using the Wave 3500 HT (Transgenomic, Inc, Omaha, Neb) and/or sequence analysis using the CEQ 8000 (Beckman Coulter, Inc, Fullerton, Calif). To test for the presence or absence of the identified mutation, family members of index cases with identified mutations underwent cascade screening by a direct mutation analysis using MGB probes by TaqMan 7000 (Applied Biosystems, Inc, Foster City, Calif).

**Genealogical Analysis**

Pedigrees for all families were constructed using Cyrilic 2.1 (Cyrilic Software, Oxfordshire, United Kingdom) and/or Progeny 7 (Progeny Software, South Bend, Ind., US) software. Genealogical investigations in Sweden are enabled by unique records of catechetical meetings dating back to the late 17th century, which annually describe births, deaths, and migration within a parish. The lineage of each index case was described based on the identification of obligate mutation carriers (OCs) by researching local parish registers, census records, and genealogical databases.

The assessment of the natural history of the LQTS mutation was done by investigating the survival beyond the age of 40 years1,13 for nonmedicated mutation carriers and their ancestors born between 1873 and 1968. Investigation was restricted to families connected by an identified common founder to minimize the number of noncarriers included. The direct line of inheritance between the common ancestor and the index cases was interpreted as constituted of OCs and their siblings as having a 50% inherent risk of carrihership (Mendelian laws of inheritance; Figure 1).

When choosing the time frame, the upper limit was restricted by the availability of complete data from records of census and the lower limit by the criteria that individuals should have turned 40 years by the year 2008. This restriction generated the actual selected time period, 1873–1968. The cause of death was investigated, using medical records and census records, whenever an individual was younger than 40 years at the time of death.

**Statistical Analysis**

All values were presented as mean, median, range, ±SD, interquartile range, or percentage. For comparison within the Y111C population, the t test was used for the numeric variables: QTc, gender, and symptoms. For comparison between LQT1 populations, the 2-sample t test was used for the numeric variables: mean follow-up before therapy, mean age at onset, and QTc. Fisher exact test was used for the nominal variables: incidence of life-threatening cardiac events, gender, symptoms at the age of <40 years, ECGs analyzed, and QTc ≤440 and ≥500 ms. The Wilcoxon signed-rank test was used for the numeric variables: median age at onset and median follow-up.

Data summarization and statistical analyses were made with software from SPSS, Inc (version 16.0, Chicago, Ill). Statistical analyses on summarized data were performed using software from Minitab, Inc (version 15, State College, Pa). All tests were 2-tailed, except the tests of the hypothesis that the incidence of ACA/SCD was lower in the Y111C population, which were lower tailed. A value of P<0.05 was considered statistically significant.

Data on incidence of life-threatening cardiac events in patients younger than 40 years at the time of death was compared with that of the published data on 386 LQT1 mutation carriers.1 Clinical data on the Y111C mutation carriers was compared with the published data on 244 A341V-KCNQ1 mutation carriers and 205 LQT1/non-A341V mutation carriers.8 Infant death rates and overall death rates derived from the historical data were compared with demographic data on age-stratified mortality rates in the Swedish population.1,4

**Ethical Considerations**

All participants or their legal guardian gave their written informed consent, and the study has been approved by the Regional Ethical Review Board at Umeå University.

**Results**

Fifteen index cases from apparently unrelated families were identified as carriers of the Y111C-KCNQ1 mutation, previ-
The mean age of mutation carriers was 28±20 years, ranging between 3 and 77 years (median age, 22.5 years). There were 44 women (55%) and 36 men (45%) in the study ranging between 3 and 77 years (median age, 22.5 years).

### Clinical Phenotype

Of the 80 Y111C mutation carriers, 24 (30%) developed symptoms before 40 years of age. In this group, 15 (62.5%) were women and 9 (37.5%) were men. Onset of symptoms occurred at 13±8 years of age (range, 4 to 37 years; median, 11 years). The age at onset in women was 14±9 years (range, 4 to 37 years; median, 12 years) and in men 12±6 years (range, 6 to 25 years; median, 11 years).

Three female mutation carriers experienced their first symptoms after 40 years of age (3 of 18, 17%), a finding that supports the concept that LQTS remains of clinical importance after the age of 40 years. Among all symptomatic Y111C mutation carriers, 33% (6 of 18 women and 3 of 9 men) experienced their first symptoms before 10 years of age, whereas 67% (12 of 18) of women and 89% (8 of 9) of men were symptomatic by 20 years of age. All symptomatic male patients experienced a first cardiac event at the age of <25 years, whereas 28% (5 of 18) of symptomatic female patients experienced a first cardiac event at the age of ≥25 years.

Reported triggers for syncopal episodes were most frequently physical exercise (56%), emotional stress (25%), and unspecific (19%), with no significant difference between the sexes. Among the 7 individuals with a debut of symptoms after 20 years of age, emotional stress and nonspecific triggers were the most common (each 37.5%), whereas exercise was least common (25%), in accordance with previous studies on genotype-specific triggers.

All symptomatic carriers presented with histories of syncope and 1 individual experienced an ACA, corresponding to an incidence of ACA among Y111C mutation carriers of 1.25%. The ACA occurred in a 13-year-old boy who had experienced episodes of syncpe with seizures 4 years previously, which was interpreted as epilepsy at that time. The ACA occurred at home and was witnessed by his mother, an ambulance paramedic, who resuscitated him. Subsequent investigation revealed a QTc of 514 ms, leading to diagnosis of LQTS, and β-blocker therapy was initiated.

### Electrocardiography

The mean QTc in all Y111C mutation carriers was 481±36 ms (range, 410 to 630 ms). QTc was classified as normal in 11 mutation carriers (14%) and as prolonged in 67 (86%). QTc exceeded 500 ms in 19 carriers (24%). Women presented with a longer QTc than men (490±40 ms versus 470±28 ms, P=0.012). QTc of symptomatic carriers was longer than the QTc of asymptomatic carriers (494±38 ms versus 474±33 ms, P=0.019). QTc of the 3 women with an age at onset >40 years was markedly prolonged (473, 532, and 630 ms).

### Comparison Between the Y111C, A341V, and LQT1/Non-A341V Populations

To examine the apparent benign phenotype of the Swedish Y111C mutation carriers (n=80), the clinical presentation was compared with the published data on the carriers of the A341V mutation (n=244), a dominant-negative KCNQ1 mutation associated with a severe phenotype (Table 2), and a genetically heterogeneous LQT1 population (n=205), not including any A341V families (Table 3).

In summary, electrocardiographic parameters were comparable for the 2 dominant-negative mutations (Y111C/A341V), whereas the clinical parameters regarding symptoms significantly differed (P<0.001). When comparing the Y111C population with the LQT1/non-A341V population, QTc was significantly longer in the Y111C population (P=0.001) whereas clinical parameters were comparable.
When testing the hypothesis that life-threatening cardiac events are less prevalent in the Y111C population, statistical significance was found in comparison with the A341V population ($P < 0.001$) and the LQT1/non-A341V population ($P < 0.045$).

**Prophylactic Treatment and Therapy**

Treatment with $\beta$-blockers was initiated in 50 (62.5%) of the mutation carriers during the follow-up. The average age at initiation of therapy was 17±17 years (median, 11.5 years).

The mean number of life-years before the initiation of therapy among mutation carriers was 25±20 years (range, 0 to 77 years; median, 19.5 years). In total, 1979 nonmedicated observable life-years were noted.

Two mutation carriers have received pacemakers because of $\beta$-blocker-induced bradycardia. One mutation carrier, an adult female, was treated with an implantable cardioverter defibrillator because of symptoms of syncope and seizures at rest despite $\beta$-blocker therapy. The patient has received no appropriate shocks in the 2 years since implantation.

**Genealogical Results**

Genealogical studies identified a common ancestor for 8 of the 15 index cases, born 11 generations previously in 1694, in an inland county in northern Sweden (Figure 2).

Ancestors of all 15 index cases have been shown to originate from the same geographic region in northern Sweden, suggesting that the occurrence of the Y111C mutation in the Swedish population could be a founder effect.

**Natural History of the Y111C Mutation**

The survival beyond the age of 40 years without therapy was investigated through ascertaining the age at death and cause of death of 107 nonmedicated individuals born between 1873 and 1968. This group included 24 genetically MCs from the study population and 83 family members. The family members, all undefined genotype, pertained to the 8 index families connected by an identified common ancestor and were born along the hypothesized line of descent of the mutation as illustrated by the pedigree (Figure 2). Of the 83 family members, 16 were OCs and 67 were siblings (S). In total, it was estimated that $\approx 73$ of the 107 individuals were mutation carriers (24 MCs + 16 OCs + 0.5 × 67 S = 73.5).

Two living MCs born before 1968 began $\beta$-blocker therapy at 34 and 35 years of age and were not included. No family member in the 8 families who were born during the actual period was excluded.

Among the 107 individuals investigated, a total of 4 individuals died at the age of <40 years. Between 1873 and 1915, 3 children younger than 1 year died, corresponding to an infant death rate of 7%. During the same period, the infant death rate in the Swedish general population was 7% to 15%. After 1915, a 4-year-old child died from acute nephritis. All 4 cases of death below the age of 40 years occurred among siblings of OCs. None of the nonmedicated genotyped mutation carriers or the OCs died before the age of 40 years (Table 4).

In 4 cases, all born in the late 19th century, age at death could not be ascertained. One man, then 18 years old, moved from his parish and could not be traced further. Information regarding the other 3 individuals, other than their date of birth, could not be found. All 4 missing cases were siblings of OCs.

In the analyzed group, the overall death rate due to any cause before the age of 40 years was 4% (4 of 107), or if assuming that all 4 missing cases died before 40 years of age,
Discussion

In this study, we found a low cumulative incidence (1.25%) of ACA among Y111C-KCNQ1 mutation carriers in the Swedish population. One case of ACA occurred in a boy harboring several reported risk factors for ACA/SCD during childhood; a preadolescent nonmedicated male patient with a QTc >500 ms and a history of previous syncpe.17 None of the 80 individuals in the study population experienced SCD during the mean follow-up time of 28±20 years, with a mean of 25±20 years before the initiation of therapy.

This finding is unexpected because the specific Y111C-KCNQ1 mutation has been shown to result in structural and functional effects on the Ks channel leading to a severely reduced inward potassium current over the cell membrane in vitro,9,10 characteristics that suggest a highly malignant mutation.

Discrepant Findings

As in the case with the 36-year-old LQT1 woman previously described, the Y111C mutation would be expected to result in a severe phenotype in all mutation carriers with respect to the electrophysiological findings.10 Indeed, the penetrance of the Y111C mutation in the Swedish population is unusually high for a LQT1 mutation.1,18 The absolute majority (86%) of the Y111C mutation carriers exhibits phenotypic effects of the mutation in the form of a prolonged QTc, which usually corresponds to an increased risk of developing symptoms. The electrocardiographic finding of a markedly prolonged mean QTc in the Y111C population is comparable with that of the A341V population; however, when comparing characteristics related to the concept of clinical severity, such as proportion of symptomatic mutation carriers (30% versus 75%, \( P<0.001 \)), median age at onset (11 versus 6 years, \( P<0.001 \)), incidence of ACA (1.25% versus 30%, \( P<0.001 \)), and SCD (0% versus 13.5%), the differences between the 2 populations are convincing.

Importantly, the apparent mild clinical phenotype of the Y111C population withstands comparison not only to the documented severe phenotype of the A341V population but also to 2 genetically heterogeneous LQT1 population.1,18 Regarding life-threatening cardiac events, the cumulative incidence was lower in the Y111C population as compared with the LQT1/non-A341V population (\( P=0.045 \)), and the incidence rate before therapy was lower than in the LQT1 population (\( P=0.025 \)), again notably with no case of SCD in the Y111C population.

Benign Natural History, 1873 to 1968

To circumvent the possible confounding role of \( \beta \)-blocker therapy,19,20 we investigated the survival beyond the age of 40 years in the Y111C population between 1873 and 1968. LQTS-related mortality in the era before \( \beta \)-blocker therapy has been reported as exceeding 50% for symptomatic individuals.21 Analogous to the 10% cumulative incidence of ACA or SCD in the LQT1 population,1 at least 7 cases (10% of 24+16+0.5×67 mutation carriers) of LQTS-related death would be expected among the nonmedicated ancestors, although surprisingly none were found. Indeed, with a total of 4 cases of death <40 years of age (1 acute nephritis and 3 infant deaths), the overall death rate (4%) was lower in the Y111C population than in the average Swedish population during that time period. Regarding the 3 cases of infant death, the role of LQTS in the sudden infant death syndrome has been much debated.22–25 Although it has been shown in a large study that LQTS mutations were present in 19 of 201 cases (9.5%) of sudden infant death syndrome, only 2 of the 15 genetic alterations identified were KCNQ1 mutations, each present in 1 case of sudden infant death syndrome, corresponding to a presence of KCNQ1 mutations in sudden infant death syndrome cases of a modest 1% (2 of 201).22

The absence of an increased mortality below the age of 40 years in nonmedicated MCs, OCs, and their siblings implies that the 1.25% cumulative incidence of life-threatening cardiac events observed in the Swedish Y111C mutation carriers is not merely a reflection of successful \( \beta \)-blocker therapy.

Functional Studies and Clinical Severity

The electrophysiological reexpression studies on the Y111C mutation were conducted by 2 separate research teams in 4 different cellular models (Xenopus oocytes, MDCK cells, COS-7 cells, and neonatal mouse cardiomyocytes) with congruent findings of severe channel dysfunction when evaluating the effect of the Y111C-KCNQ1 mutation in vitro.9,10

The point mutation (c.332A>G) leading to an amino acid substitution (Y111C) alters a motif in the N-terminal protein that plays a key role in the trafficking of the Ks channel. This alteration results in intracellular retention of the channel that renders it inactive.9,10 The dominant-negative effect of the Y111C mutation is mediated by the prevention of transport of channels assembled from both mutated and wild-type subunits. The synergistic inhibition of normal Ks-channel localization and function produces a loss of repolarization current exceeding 75% in the in vitro setting.10

In a recent study on 356 LQT1 mutation carriers with known or suspected alterations in the ion-channel function, it was demonstrated that the degree of channel dysfunction in vitro was a major risk factor for cardiac events, independent of clinical risk factors and \( \beta \)-blocker therapy.11 However, it has been recently proposed that cellular electrophysiological studies cannot always predict the clinical phenotype of a mutation; despite the severe clinical pheno-
type of the A341V mutation carriers, only a mild dominant negative effect was demonstrated in vitro.\textsuperscript{7,8}

It is evident that clinical observations should modulate the interpretation of experimental findings. It is, however, unclear how the pronounced discrepancy between the in vitro and clinical phenotype in the Y111C population should be interpreted.

Potential Role of Modifying Factors

A complex influence on phenotype by genetic, epigenetic, and environmental modifying factors is to be expected in any LQTS population. The concept of modifier genes, including compound heterozygosity\textsuperscript{26} and the addition of single-nucleotide polymorphisms (SNPs)\textsuperscript{27,28} to LQTS mutations, has been proposed to explain the phenomenon of phenotypic heterogeneity.\textsuperscript{29} Although modifier genes have previously been reported in the context of amplifying the effect of LQTS mutations,\textsuperscript{26–28} a recent study has provided some evidence that SNPs might ameliorate the clinical phenotype of a LQTS mutation.\textsuperscript{30}

A possible explanation to the discrepancy between in vitro and clinical phenotype found in the Swedish Y111C population could be the existence of a modifying SNP that very closely accompanies the deleterious mutation in these individuals. The SNP would hence be situated within the same haplblock as the mutation, passed on to the descendants from a common founder. The Swedish Y111C population is a proposed founder population, based on genealogical and geographic evidence,\textsuperscript{31} theoretically connected by a single common ancestor.

Although the existence of a protective modifier SNP as an explanatory model for our findings is improbable, implying a transmission of said SNP of nearly 100%, the possibility is intriguing. Dahimene et al\textsuperscript{32} reasoned that a correction of the trafficking defect caused by the Y111C mutation might be possible by chemical and molecular chaperones. Induction of such facilitating proteins could be a possible mechanism of action for genetic modifiers in this population. Further studies are needed to identify potential modifying factors.

Limitations

There are obvious limitations in performing comparisons with summarized data published by other authors because of variations in methodology and study populations. This should be taken into account when evaluating the results of the statistical analyses, and the probability values presented here should therefore be interpreted with care.

Despite excellent records of census in northern Sweden, the reliability of historical data are inherently limited. There is a need for formal evidence in the form of microsatellite markers to define that the occurrence of the Y111C-KCNQ1 mutation in the Swedish population is indeed a founder effect.

In this study, not all major LQTS genes were sequenced when investigating the genotype of the index cases, and 5 index cases were identified by mutation analysis only, precluding the possibility of identifying individuals carrying a second mutation.

Conclusions

We have, by investigating the phenotype of 80 Y111C-KCNQ1 mutation carriers as well as the natural history of the mutation in their nonmedicated ancestors, revealed a low incidence of life-threatening cardiac events in the Swedish Y111C population. The finding is the more intriguing taking into account the strong dominant-negative effect\textsuperscript{30} and high penetrance of the specific Y111C-KCNQ1 mutation.

Our findings confirm that clinical reality cannot always be predicted by in vitro studies and support the concept that the current assessments of the electrophysiological effects of LQTS mutations does not provide all the elements necessary for a valid genotype-phenotype correlation.\textsuperscript{8} In conclusion, our findings emphasize the importance of clinical observations in the risk stratification of the LQTS.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

In this study, we have characterized the clinical phenotype of a Swedish Y111C type 1 long-QT syndrome sample and observed a low risk of life-threatening cardiac events, despite a markedly prolonged QTc. The Y111C mutation is currently the single most common type 1 long-QT syndrome–causing mutation in Sweden, and knowledge of the natural history and mutation-specific phenotypic characteristics of this population is important for risk stratification and clinical management, especially for providing information and education to the affected families. The finding of a low incidence of life-threatening cardiac events and no case of sudden cardiac death in this sample, despite the severe electrophysiological profile of the Y111C mutation demonstrated in vitro, constitutes an important contribution to the current debate regarding in vitro versus clinical research in type 1 long-QT syndrome. The discrepancy found supports the concept that the current assessments of the electrophysiological effects of type 1 long-QT syndrome mutations may not provide all the elements necessary for a valid genotype-phenotype correlation. In conclusion, our findings emphasize the importance of clinical observations in the risk stratification of the long-QT syndrome.
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