Prevalence of the Congenital Long-QT Syndrome

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Background—The prevalence of genetic arrhythmogenic diseases is unknown. For the long-QT syndrome (LQTS), figures ranging from 1:20000 to 1:5000 were published, but none was based on actual data. Our objective was to define the prevalence of LQTS.

Methods and Results—In 18 maternity hospitals, an ECG was performed in 44 596 infants 15 to 25 days old (43 080 whites). In infants with a corrected QT interval (QTc) >450 ms, the ECG was repeated within 1 to 2 weeks. Genetic analysis, by screening 7 LQTS genes, was performed in 28 of 31 (90%) and in 14 of 28 infants (50%) with, respectively, a QTc >470 ms or between 461 and 470 ms. A QTc of 451 to 460, 461 to 470, and >470 ms was observed in 177 (0.41%), 28 (0.06%), and 31 infants (0.07%). Among genotyped infants, disease-causing mutations were found in 12 of 28 (43%) with a QTc >470 ms and in 4 of 14 (29%) with a QTc of 461 to 470 ms. One genotype-negative infant (QTc 482 ms) was diagnosed as affected by LQTS on clinical grounds. Among family members of genotype-positive infants, 51% were found to carry disease-causing mutations. In total, 17 of 43 080 white infants were affected by LQTS, demonstrating a prevalence of at least 1:2534 apparently healthy live births (95% confidence interval, 1:1583 to 1:4350).

Conclusions—This study provides the first data-based estimate of the prevalence of LQTS among whites. On the basis of the nongenotyped infants with QTc between 451 and 470 ms, we advance the hypothesis that this prevalence might be close to 1:2000. ECG-guided molecular screening can identify most infants affected by LQTS and unmask affected relatives, thus allowing effective preventive measures. (Circulation. 2009;120:1761-1767.)

Key Words: arrhythmia ■ death, sudden ■ electrocardiography ■ genetics ■ long-QT syndrome

The last 15 years have witnessed growing and widespread interest in arrhythmogenic diseases of genetic origin. These cardiac disorders are regarded as rare, but their prevalence remains unknown. The case of the long-QT syndrome (LQTS) is paradigmatic. One of the leading contributors to sudden death in the young, LQTS is caused by mutations in genes encoding ion channels involved in the control of ventricular repolarization. After the identification of the first 3 major LQTS genes,1-3 the list now includes 12 disease-causing genes.4-8 Fifty years have elapsed since LQTS was described in its 2 variants with9,10 and without11-13 congenital deafness, but no reliable data exist on its prevalence. The literature offers a variety of rates, ranging from 1:20 000,14 to 1:10 000,15 to 1:5000.16,17 These very different rates of prevalence are at best educated guesses not supported by any actual data.

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Clinical Perspective on p 1767

A recently completed large prospective ECG study in 3- to 4-week-old infants provides the first opportunity for a data-driven assessment of the prevalence of LQTS. Over a period of

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30 years, between 1976 and 2007, after our initial suggestion, we and others had demonstrated that ≈10% to 15% of cases of sudden infant death syndrome may actually be caused by LQTS. Because death could be prevented in these infants by an early diagnosis and especially because a significant portion of sudden deaths among LQTS patients represents the first manifestation of the disease, the Italian Ministry of Health has considered following our recommendation of introducing a program of neonatal ECG screening as part of the National Health Service, with early identification of most cases of LQTS as the main objective. Accordingly, they requested and funded a prospective study to obtain relevant information. This study, completed recently with the enrollment of 44 596 neonates, has indicated that such a program would be highly cost-effective in Europe. In the infants with a marked QT interval prolongation confirmed in 2 different ECGs, we performed molecular screening with the objective of obtaining a reliable estimate of the prevalence of LQTS.

Methods

Study Population
The population under study included 44 596 neonates (43 080 whites), 22 967 males (51%), and 21 629 females (49%) consecutively enrolled by 18 maternity hospitals (see Appendix in the online-only Data Supplement) between January 2001 and June 2006, in whom an ECG was recorded between the 15th and the 25th day of life. At hospital discharge, the parents were asked to return with their babies to perform an ECG and to complete a questionnaire with personal and clinical data. In no case was the ECG performed because of the presence of LQTS in the family. All neonates were apparently healthy because very premature and sick newborns were usually transferred to intensive care units before they could be enrolled. All parents signed an informed consent. Our records show no refusals of the ECG screening by the parents.

Electrocardiography
Twelve-lead ECGs were recorded at a paper speed of 25 mm/s with a Marquette MAC 5000 recorder. The ECGs were initially analyzed in the participating centers and, because written reports had to be prepared, they were measured manually. All ECGs were then transferred via modem together with personal and clinical data through a dedicated Web site to the Coordinating Center, where they were all reread manually, first those with a corrected QT interval (QTc) >470 ms, a blood sample was taken from the neonate and from his or her parents for genetic analysis. Toward the end of the study, it was decided to extend the genetic analysis to the infants with a QTc between 461 and 470 ms.

Genetic Analysis
With informed consent (institutional review board of our university hospital), genomic DNA was extracted from peripheral blood lymphocytes obtained from the proband and first-degree relatives by standard methods. All coding exons of KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, CAV3, and SCN4B (the genes currently screened in our laboratory for the routine diagnosis of LQTS) were amplified by polymerase chain reaction with the use of previously published primer pairs or home-designed primers. Amplicons were screened for sequence variants with the use of denaturing high-performance liquid chromatography analysis performed on 2 different automated DNA fragment analysis systems (Wave models 1100 and 3500HT, Transgenomic, San Jose, Calif). Elution profiles were compared with normal control products. Results exhibiting divergent chromatographic profiles were purified enzymatically (ExoSAP-IT, Amersham Bioscience, Piscataway, NJ) and sequenced with the use of fluorescent dye terminator chemistry (Big-Dye Terminator system, Applied Biosystems Inc, Foster City, Calif).

All the genetic variants identified were searched in a population of 300 ethnically matched controls (all whites) and in all available online databases. A genetic variant was regarded as a disease-causing mutation if it had been already described in other LQTS families and/or if a functional study was available to prove its functional effect. In case of a novel mutation, we evaluated its absence in control populations, the conservation among different species, the presence of a genotype-phenotype correlation among family members, and whenever possible its functional effect through a cellular electrophysiological study.

Statistical Analysis
The distribution of values for heart rate, QT interval, and QTc was assessed, and percentile values (2.5th and 97.5th) were calculated. Differences in ECG measurements between groups were assessed by Student t test. Prevalence data are reported as proportions of subjects with confirmed LQTS along with binomial exact 95% confidence intervals. Given the fact that all 300 controls were whites, it was conservatively decided to calculate prevalence only in the 43 080 whites, a group that represents 97% of the population under study and the one in which all genetic variants had been identified. Data are presented as mean±SD. A 2-sided P value <0.05 was considered statistically significant.

Results

ECG Characteristics
Heart rate, QT interval, and QTc values were normally distributed. Mean heart rate was 153±16 bpm, mean QT interval was 256±18 ms, and mean QTc was 406±20 ms and was slightly longer in females than in males (407±20 and 405±20 ms; P<0.001). The 97.5th and the 2.5th percentiles, defining the upper and lower normal values, were 443 and 364 ms, respectively.

Neonates With QT Interval Prolongation
The QT interval was considered prolonged according to the guidelines for the interpretation of neonatal ECG of the European Society of Cardiology. In 1094 neonates (2.5%) QTc was >440 ms, and in 858 (2.0%) it was between 441 and 450 ms, an area that, for the purpose of this study, we regarded as borderline prolonged. There were 177 infants with a QTc between 451 and 460 ms, 28 between 461 and 470 ms, and 31 >470 ms (Figure 1). Among these 31 neonates (1:1438; 0.07%; 23 females and 8 males), 4 had a QTc >500 ms.

Two of the 31 neonates with a QTc >470 ms did not return for the second ECG and were lost to follow-up. In all remaining 29 neonates, QT interval prolongation was confirmed at the second ECG, which showed a QTc >470 ms in 26 and between 461 and 470 in 3. Mean QTc was 485±17 ms on the first ECG and 484±20 ms on the second. These infants were managed according to the guidelines in consideration of their risk for sudden infant death syndrome. They underwent an echocardiogram, which was normal in all cases, and a 24-hour ECG Holter recording that confirmed the QT interval prolongation and showed no arrhythmias. All but 1, because of parental refusal, were then treated with propranolol 2 mg/kg per day, and none of them experienced side effects. During follow-up (median, 2.8; range, 0.7 to 6.9 years), they all remained free of symptoms.
The neonates with a QTc between 461 and 470 ms were followed with additional ECGs, according to the guidelines. In all cases, the second ECG essentially confirmed the QTc values observed on the first ECG. Two of them were treated with propranolol because of further QTc prolongation on a 24-hour Holter recording.

**Genetic Analysis in the Neonates With Markedly Prolonged QT Interval (>470 ms)**

Blood samples for DNA extraction and molecular analysis were obtained in 28 of 29 neonates (96%) with QTc >470 ms (7 males and 21 females) available during follow-up; the parents of 1 subject did not consent to genetic analysis. LQTS mutations were identified in 12 of 28 neonates (43%): 8 were carrying heterozygous mutations on the KCNQ1 gene (LQT1) and 4 on KCNH2 (LQT2). The distribution among the LQTS subgroups confirmed the higher prevalence of LQT1, similar to our report from the Pavia database, and most of the mutations identified had already been described in other LQTS families. The Table provides the information relevant to all the mutations identified and

<table>
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<tr>
<th>LQTS Mutations</th>
<th>Sex</th>
<th>QTc</th>
<th>Inheritance</th>
<th>Mutation Carriers Among Family Members, n (%)</th>
<th>Mutation Characteristics†</th>
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*Probands not included.
†A indicates already known LQTS mutation; B, functional effect; and C, positive genotype-phenotype correlation among family members.
‡Associated with KCNE1-D85N, KCNE1-S38G, KCNH2-K897T, and SCN5A-H558R.

Figure 1. Distribution of the 43,080 white neonates among 5 subgroups (absolute numbers and percentage), according to QTc duration on the screening ECG. Neonates positive at the genetic analysis are also reported.
regarded as causing disease. A novel SCN5A genetic variant (A647V), located in a highly conserved region and never reported in controls, was identified in an infant but was not regarded as causing disease and not included among the LQTS-related mutations because the same mutation was found in the infant’s father and grandmother, who were asymptomatic and had a normal QTc. Furthermore, our own cellular electrophysiological study failed to show functional effects. Additionally, to be very conservative, we did not include the SCN5A-P2006A, which we identified in 1 of 300 controls. However, we suspect that P2006A might play some contributory role not only because it has a functional effect but also because we found it in 2 victims of sudden infant death syndrome and in 1 stillbirth. On this basis, we decided not to consider these 2 variants as related to LQTS.

Among the neonates with negative genotyping, the father of 1 infant with a QTc of 482 ms also had an extremely prolonged QTc (581 ms). These 2 ECGs, taken together, are diagnostic for LQTS even in the absence of symptoms; accordingly, we considered this neonate as definitely affected by LQTS despite negative genotyping. Currently, in patients with definite LQTS, no mutations are identified in the 7 genes regularly screened in our laboratory: QTc was longer in neonates found to have a mutation than in those with negative genotyping (494±24 versus 479±5 ms; P=0.049). If individual values are considered, LQTS mutations were identified in 6 of 7 neonates with a QTc >485 ms.

Genetic Analysis in Neonates With Prolonged QT Interval (461 to 470 ms)

Blood samples for DNA extraction and molecular analysis were obtained from 14 of the 28 neonates (50%) with a QTc between 461 and 470 ms, and LQTS mutations were identified in 4 of 14 neonates (29%). When these 4 mutations are added to the 12 identified among infants with a QTc >470 ms, the total number of disease-causing mutations becomes 16. Details are provided in the Table.

One infant carried 2 independent mutations: The first was an already described LQTS mutation in the C-terminal region of KCNH2 (R922W), and the second was a novel one in the extracellular loop between S3 and S4 of KCNQ1 (T224M). One infant carried a novel mutation in the N-terminal region of KCNH2 (D102V). In both of these cases, the genotype segregated with the clinical phenotype among family members. In the remaining 2 cases, a mutation in KCNE1 (S28L) and KCNE2 (I57T), respectively, was identified; both had already been described and 1 had also been functionally characterized (Table). In the infant with the KCNE2-I57T mutation, normalization of the QTc was observed at follow-up, suggesting a mild form of LQTS that could manifest itself mainly as a predisposition to drug-induced torsades de pointes, as reported previously.

Mutation Status and QTc Normalization

QTc normalization at 1 year of life occurred in 3 of 16 genotype-positive (19%) and in 24 of 25 genotype-negative infants (96%) with an available ECG at follow-up. Importantly, the only genotype-negative child in whom QTc remained prolonged was the one whose father also had marked QT prolongation and who was considered affected by LQTS on clinical criteria. Among the 14 infants whose QT interval remained prolonged at 1 year of life, a disease-causing mutation was identified in 13 (92%).

Genetic Analysis in Parents and Family Members

In all 16 cases with LQTS mutations, genetic analysis was extended to the parents. Only 1 case was a de novo mutation, whereas in the others the mutation was inherited from the father (n=8) or from the mother (n=7), in whom LQTS had not been diagnosed previously. The analysis was then performed in other family members, and it allowed the identification of 42 of 82 mutation carriers (51%). QTc was prolonged in 32 of 42 mutation-positive subjects (76%); some family members had striking QT prolongations unrecognized previously (Figure 2). The family members affected by LQTS had not been diagnosed previously; most of them, following our recommendation based on the European guidelines, are now treated with β-blockers and continue to remain free of symptoms, with 1 exception. A young man in his early 20s, a member of the family with the KCNH2-R744X mutation, did not take the recommended β-blockers and actually initiated antimalaria prophylaxis; he was found dead in his bed. Because the autopsy was negative, this sudden death was likely caused by the combination of a QT-prolonging drug with a disease-causing LQTS mutation.

Prevalence of LQTS

Our data clearly indicate that at least 17 infants (16 because of disease-causing mutations and 1 because of clear-cut clinical diagnosis) among this cohort of 44 596 neonates are affected by LQTS. All of them are white. This indicates a prevalence among whites of 1:2534 (95% confidence interval, 1:1583 to 1:4350). This prevalence is much higher than that suggested previously.

Discussion

The present findings provide the first data-based estimate of the prevalence of a clinically important arrhythmogenic disease of genetic origin, the LQTS. Until now, prevalence of these diseases, regarded as “rare,” was simply unknown despite the fact that articles and textbooks often mentioned one or another estimate but without support from objective data. Our own data, based on ECG-guided identification of disease-causing mutations, indicate that among whites, the prevalence of LQTS is at least 1:2534 apparently healthy live births. This finding has direct implications for the early detection of LQTS.

QT Interval Prolongation and Probability of Carrying LQTS Mutations

Besides it being an intuitive concept, our data point to a positive correlation between duration of the QT interval and probability of carrying LQTS disease-causing mutations. This is already evident in the group with marked QT prolongation because among all infants with a QTc >470 ms, this probability was 43% (12/28), but it increased to 86% (6/7) in the neonates with a QTc >485 ms. Moreover, the probability of finding disease-causing mutations in the 7 genes tested was 92% among the infants whose QTc was >470 ms initially and remained prolonged >450 ms at 1 year of life.
Among the infants with a QTc between 461 and 470 ms, 4 of 14 (29%) had disease-causing mutations, but for 14 of 28 we did not obtain blood for genetic analysis. Considering the possibility that among the nongenotyped 196 infants with a QTc between 450 and 470 ms there might be some LQTS mutation carriers, we advance the hypothesis that the prevalence of LQTS may be closer to 1:2000.

Our study cannot answer the question of how many neonates carry LQTS mutations in the presence of a normal or borderline prolonged (between 441 and 450 ms) QT interval. In 1975, we suggested that “LQTS is more unrecognized than rare,” and in 2003, we pointed to the until then unsuspected high frequency of patients carrying 2 independent mutations of maternal and paternal origin (“compound mutations”) as further evidence of a relatively frequent presence of LQTS mutations in the general population. In 1999, supported also by previous suggestions, we provided the evidence for the existence of low penetrance in LQTS, which implied the presence of many “silent” mutation carriers (ie, subjects with disease-causing mutations but with a QTc within normal limits [<440 ms]).

The number of silent mutation carriers cannot be assessed in the general population because it would require mass molecular screening, which is practically unfeasible. We have previously indicated that their percentage varies within the main genotypes, being high (36%) among LQT1 patients and decreasing progressively among LQT2 (17%) and LQT3 (10%) patients. It is unavoidable that the prevalence of LQTS will remain an underestimate because it has to refer to LQTS with QT prolongation and cannot include clinically silent mutation carriers. However, and of clinical relevance, the risk of spontaneous major cardiac events among LQTS patients with a normal QT interval is very modest; their main risk is the exposure to drugs with Ik,C-blocking activity with the attendant possibility of developing torsades de pointes ventricular tachycardia.

**Study Limitations**

The present data suffer from a significant limitation, which has its origin in the design of the study. We initially decided to follow the recommendations of the European guidelines (of which we share responsibility) and to plan the genetic screening only for infants with a QTc >470 ms. When we realized that mutation carriers were likely to also be found among infants with a less marked QT prolongation, it was too late in some respects. Indeed, despite our efforts, it proves difficult to trace all the families involved and, when we succeed, to convince the parents of apparently healthy children to return for genetic testing.

At first glance, another potential limitation might arise from the fact that the present study was conducted entirely in Italy, thus raising questions about the legitimacy of using the same figures and their relevance to other populations. As a matter of fact, the figures obtained for the Italian population can be expected to be comparable to those found in Europe, at least for countries sharing similar historical background. It is important to realize that Italians, with the exception of the inhabitants of the island of Sardinia, do not constitute an “ethnic group.” Historical reasons, beginning with the initial large movements of populations coming through the Middle East and then settling into Europe and especially continuing with the “barbaric” invasions of the first thousand years of the modern era, which were characterized by the fact that the “barbarians” instead of returning to Central Europe kept settling in Italy and mixing with the friendly local inhabitants, have resulted in the fact that the genetic characteristics of the Italians are largely similar to those of most other European countries. For the same reasons, the prevalence estimated in Italy may also be a reasonable estimate for the North American population of European descent.

**Implications**

Besides providing the first direct evidence on the prevalence of LQTS, which is much higher than previously postulated, these
findings carry clinically relevant implications. One is that infants with a QTc >460 ms in the first month of life and whose QT interval remains prolonged at 1 year have a >90% probability of carrying a LQTS-causing mutation. In addition, whereas genetic screening should be performed immediately in all infants with a QTc >485 ms, the normalization within a year for 75% of the infants with an initial QTc between 460 and 485 ms suggests, unless 1 of the parents shows QT prolongation, postponement of the genetic screening for this group until the end of the first year of life. This simple measure will reduce both costs and unnecessary anxiety.

Another major implication, in a still controversial area, is that a very feasible and relatively inexpensive ECG screening would identify most of the neonates affected by LQTS. Moreover, this would guide molecular screening, which, in turn, because most of these are familial cases, would unmask many affected relatives (approximately half of the family members), thus allowing effective preventive measures. In the United States alone, with >4 million live births per year, this would mean at least 2000 new cases and families per year. Furthermore, this knowledge will allow health authorities in countries with a prevalent white population to estimate the number of new LQTS patients they may expect every year and to assess approximately the number of LQTS patients who may be living in their countries.

The implications for the prevention of avoidable sudden deaths in the young are evident. The tragic case of the youngster who died suddenly while on antimalaria prophylaxis is a sad reminder of the life-threatening potential of the LQTS mutations found in apparently healthy newborns and present in their apparently healthy family members. It also is consistent with the very recent evidence of the frequently devastating effect of QT-prolonging drugs administered to LQTS patients.

One final practical question concerns the best time for the ECG screening because the not uncommon QT normalization by 1 year of age could make this period of life a reasonable choice. At 1 year of age, there would be fewer false-positives, but the infants with major QT prolongation, possibly at high risk for sudden infant death syndrome between months 2 and 6, would be missed, and avoidable tragedies would not be prevented. With errors unavoidable on both sides (3 to 4 weeks versus 1 year), we would prefer to err on the safe side and not miss the very-high-risk infants. Of course, this “safety-first” approach comes with a price.

Conclusion

The actual data from this study demonstrate that, among whites, the prevalence of LQTS is at least 1:2534 apparently healthy live births.

Acknowledgments

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

This prospective ECG study, performed in 44 596 infants 15 to 25 days old and complemented by molecular screening in those with a markedly prolonged QT interval, indicates that the prevalence of the long-QT syndrome (LQTS) among whites is 1:2534 live births (95% confidence interval, 1:1583 to 1:4350), which is much higher than suspected previously. Furthermore, reasonable inferences on the infants with a prolonged QT interval who were not genotyped suggest that this prevalence may be close to 1:2000 live births. This is the first data-based estimate of the prevalence of an arrhythmogenic disease of genetic origin. As such, it will allow health authorities in countries with a prevalent white population to estimate the number of new LQTS patients they may expect every year and to assess approximately the number of LQTS patients who may be living in their countries. Of note, 51% of the family members of the affected infants were also mutation carriers. The study carries practical implications. Infants with a corrected QT interval >460 ms in the first month of life and whose corrected QT interval remains prolonged at 1 year have >90% probability of carrying a LQTS-causing mutation. Whereas genetic screening should be performed immediately in infants with a corrected QT interval >485 ms, the normalization within 1 year for 75% of the infants with a corrected QT interval between 460 and 485 ms may suggest postponement of their genetic screening until the end of their first year of life. ECG-guided molecular screening can identify most infants affected by LQTS and unmask affected relatives, thus allowing the early institution of effective preventive measures.
Prevalence of the Congenital Long-QT Syndrome
Peter J. Schwartz, Marco Stramba-Badiale, Lia Crotti, Matteo Pedrazzini, Alessandra Besana, Giuliano Bosi, Fulvio Gabbarini, Karine Goulene, Roberto Insolia, Savina Mannarino, Fabio Mosca, Luigi Nespoli, Alessandro Rimini, Enrico Rosati, Patrizia Salice and Carla Spazzolini

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APPENDIX

List of Maternity Hospitals and responsible physicians participating in the study


*deceased