

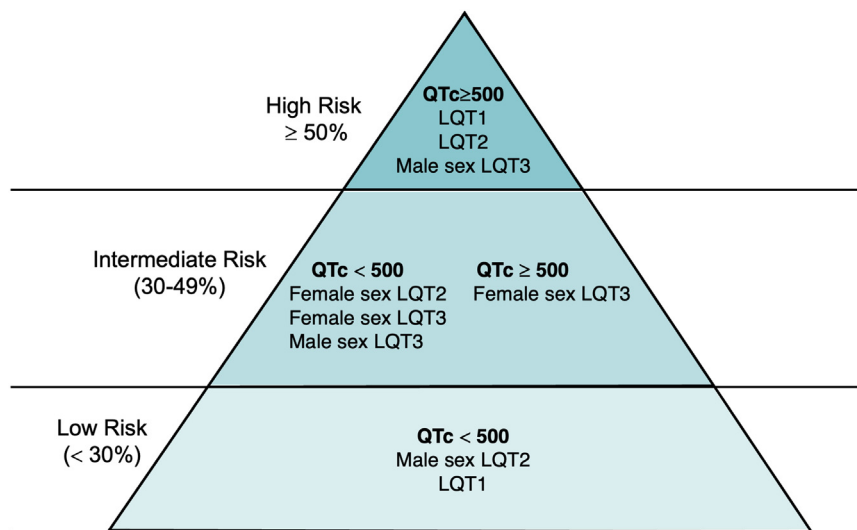


Iconic Figure

Risk stratification in long QT syndrome

Silvia G. Priori, MD, PhD, Carlo Napolitano, MD, PhD

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**Figure 1**

Proposed scheme for risk stratification in patients with LQT syndrome according to genotype and sex. LQT1, 2, 3 = long QT syndrome type 1, 2, 3; QTc = heart rate-corrected QT. Reproduced from Priori and colleagues,¹ *The New England Journal of Medicine*, Copyright © 2003 Massachusetts Medical Society. Reprinted with permission.

For several decades, long QT syndrome (LQTS) was considered a disease caused by the spatially imbalanced distribution of cardiac innervation. This theory persisted until advancements in molecular genetics revolutionized the field.

The pioneering scientist who brought about a conceptual revolution in the field was Dr Mark Keating at the University of Utah. His collaboration with Dr G Michael Vincent, as well as with the investigators of the International Long QT Syndrome Registry coordinated by Dr Arthur Moss and Dr Peter Schwartz, provided access to valuable blood samples of LQTS-affected patients. Within a few years, Dr Keating brought about the “molecular revolution” through a handful of prestigious publications, which led to the understanding of the pathogenesis of life-threatening arrhythmias in LQTS.^{1–5} The

remarkable paradigm shift induced by the scientific contributions of Dr Keating, together with his collaborators Mike Curran, Igor Splawsky, and Qing Wang, culminated within a few years as they mapped 3 LQTS loci: LQTS type 1 on chromosome 11p15.5 (*KCNQ1*), which encodes the potassium channel that conducts I_{Ks} (the slow component of the cardiac delayed rectifier current); LQTS type 2 on chromosome 7q35–36 (*HERG*), which encodes the potassium channel that conducts I_{Kr} (the rapid component of the cardiac delayed rectifier current); and LQTS type 3 on chromosome 3p21–24 (*SCN5A*), which encodes the cardiac sodium channel. Because of this novel vision and understanding of the mechanisms that lead cardiac cells harboring genetic mutations to develop ventricular fibrillation, we anticipated

From the Molecular Cardiology, ICS Maugeri and Department of Molecular Medicine, University of Pavia, Pavia, Italy.

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the opportunity to interpret the clinical data collected from our patients from a molecular perspective.

The publication of the studies by Dr Keating and his group turned into a most exciting experience for me and my colleague Carlo Napolitano. At the time when the discoveries of the Keating laboratory were first published, we were working in the outpatient clinic dedicated to patients with LQTS at the University of Pavia, with the perspective that a completely innovative field had just emerged. The anticipation that novel approaches to patient management, therapy selection, and risk stratification had become possible fueled our desire to learn and fully master the new fields of molecular biology and medical genetics. The desire to dive deep into molecular biology grew so strong that we joined Andrea Ballabio's molecular genetics laboratory in Milan. After 2 years of training, we returned to the University of Pavia with the goal of understanding the role of genetic variants in patient prognosis, a study that led to the development of "iconic figure" described here.

Our study, based on 647 patients with LQTS, focused on determining the cumulative probability of experiencing a *first cardiac event*, defined as the occurrence of syncope, cardiac arrest, or sudden death, before the age of 40 years and before the initiation of therapy. Risk was assessed according to genotype, sex, and heart rate-corrected QT interval (QTc interval). Within each genotype, we further assessed risk across 4 categories derived from the combination of sex and QTc interval (<500 or \geq 500 ms) (Figure 1).

The results showed that the prevalence of a first cardiac arrest was lower in patients with a mutation at the LQTS type 1 locus (30%) than in those with a mutation at the LQTS type 2 locus (46%) or those with a mutation at the LQTS type 3 locus (42%) (Fisher exact, $P < .001$). The multivariate analysis demonstrated

that the locus of the causative mutation independently affects the clinical course of LQTS and modulates the effects of the QTc interval and sex on clinical manifestations.

We still recall the excitement we felt when the data from Keating's laboratory were published and the irrevocable decision we made to give up our academic salaries to return to training in Ballabio's molecular genetics laboratory. This decision profoundly reshaped our careers, and we consider it the best professional decision of our lives. Even after decades, genotype-specific risk stratification continues to be adopted in clinical practice.

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Address reprint requests and correspondence: Dr Silvia G. Priori, Department of Molecular Medicine, University of Pavia, Via Maugeri 10, Pavia 27100, Italy. E-mail address: silvia.priori@icsmaugeri.it

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