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Arrhythmia Risk in Long-QT Syndrome: Beyond the Disease-Causative Mutation

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Congenital long QT syndrome (LQTS) is a genetically heterogenous disorder of myocardial repolarization that affects an estimated 1:2000 individuals and often manifests clinically as a prolonged heart rate-corrected QT interval (QTc) on ECG and an increased proclivity for torsadogenic-mediated syncope, seizures, and sudden death.[1] From a genetic perspective, LQTS has been considered classically an autosomal dominant genetic disorder, with heterozygous mutations in the three major LQTS-susceptibility genes accounting for roughly 75% of clinically robust, non-syndromic LQTS cases (*KCNQ1*/LQT1, 30%–35%; *KCNH2*/LQT2, 25%–30%, and *SCN5A*/LQT3, 5%–10%).[2,3] However, since the identification of the three major LQTS-susceptibility genes in 1995 and 1996, it has become clear that LQTS, like many other monogenic/Mendelian disorders, is at best described as an autosomal dominant disorder with marked incomplete penetrance and variable expressivity whereby related individuals who harbor the same LQTS-causative mutation often assume vastly different clinical courses in terms of QTc duration and frequency of cardiac events.[4]

In retrospect, strong evidence for this extensive phenotypic variability in LQTS was encountered long before the specific ion channel genes were implicated in the pathogenesis of the disorder. In 1992, four years before *KCNQ1* was identified as the culprit, LQT1-causative gene residing within the chromosome 11p15.5 genetic locus, Vincent et al described both a significant overlap in the range of QTc values between 11p15.5 locus carriers (410 to 590 ms; mean 490 ms) and non-carriers (380 to 470 ms; mean 420 ms) and marked variability in the frequency/severity of cardiac events between carriers of the same 11p genetic marker (63% with syncope; 5% with sudden cardiac arrest).[4, 5] Subsequent studies, including those involving large founder populations such as the South African KCNQ1-A341V LQT1 kindred, went on to demonstrate that very few LQTS-causative mutations completely escape the genetic phenomena of incomplete penetrance and variable expressivity indicating that the observed phenotypic variability in LQTS is not solely dependent on the relative strength or weakness of discrete LQTS-causative mutations, but also on the genetic background in which these mutations reside.[6]

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Naturally, given the strong correlation between the degree of QT interval prolongation and risk of cardiac events, cardiovascular mortality, and or all cause mortality in LQTS patients[7] and otherwise healthy individuals[8, 9], the elucidation of the genetic elements that modulate the phenotypic severity associated with a given LQTS-causative mutation as well as QT interval duration in otherwise healthy individuals has garnered considerable interest in recent years. Early genetic modifier studies largely utilized a candidate variant/gene approach to test the association between common single nucleotide polymorphisms (SNPs) in genes that encode either cardiac ion channels or proteins known to directly modulate their function and QTc duration and or risk of cardiac events.[4] While these studies demonstrated that common amino acid-altering SNPs in the known LQTS-susceptibility genes such as KCNE1-D85N[10], KCNH2-K897T[11], and SCN5A-H558R[12, 13] exert modest electrophysiologic effects that can modulate the *in vivo* or *in vitro* phenotypic expression of certain LQTS-causative mutations as well as modify QTc duration in LQTS patients and the general population (summarized in Table 1), these findings collectively account for only a small fraction of the phenotypic variability observed within many multigenerational LQTS families.

More recently, genome-wide association studies (GWAS) that assay massive numbers of common SNPs spread evenly throughout the human genome have provided a systematic and unbiased means of identifying QT-modulating genetic loci in the general population. In addition to providing further support for the association of KCNE1-D85N, KCNH2-K897T, and several non-coding SNPs in established LQTS-susceptibility genes with QTc duration, these studies and their subsequent meta-analyses have indentified additional novel genetic loci believed to modulate QTc duration in the general population (Table 1).[14, 15]

While one might expect that these novel genetic loci would represent a treasure trove for translational studies in congenital LQTS, thus far only SNPs in the *NOS1AP*-encoded nitric oxide synthetase 1 adaptor protein have been shown to modulate LQTS disease severity. Interestingly, studies from both the aforementioned South African KCNQ1-A341V LQT1 kindred[16] as well as a prospective registry of 901 LQT1, LQT2, and LQT3 patients with an array of LQTS-causative mutations[17] have shown that the minor alleles of two non-coding SNPs (rs4657139 and rs16847548) in *NOS1AP* are associated with both QTc prolongation and an increased risk of cardiac events in a patient with congenital LQTS.

It is in this greater context, that the study by Guicheney et al in the current issue of *Circulation: Cardiovascular Genetics* tested 112 matched symptomatic-asymptomatic LQT1/LQT2 patient duos derived from French, Italian, and Japanese LQTS cohorts for an association between LQTS disease phenotype and the presence of 25 high pre-test probability SNPs that had been associated previously with either an increased risk of cardiac events in LQTS patients or modulation of QTc duration in the general population.[18] Briefly, using this novel approach, Guicheney et al demonstrate for the first time that the minor allele of an intronic SNP (rs2074238) in *KCNQ1*, previously associated with shorter QTc intervals in the general population[14,15], confers a protective effect against cardiac events in LQTS patients.[18] Importantly, this finding was validated in a replication cohort consisting of 336 LQT1 patients from South African KCNQ1-A341V and Finnish KCNQ1-G589D founder populations, suggesting that at the very least the *KCNQ1* rs2074238 SNP attenuates the LQT1 disease phenotype in multiple genetic backgrounds.

While Guicheney et al show a clear and substantiated protective role for *KCNQ1* rs2074238 in LQT1 and possibly LQT2, perhaps surprisingly, the *KCNQ1* rs2074238 SNP represents one of only 2 LQTS modifying SNPs. The other SNP with a positive association in both the patient duos and the replication cohort was *NOS1AP* rs12029454, which interestingly is not one of the two the *NOS1AP* SNPs shown to modulate LQTS disease severity in previous

studies. The other 23 QT-modifying/disease-modifying SNPs (Table 1) failed to modify the disease phenotype of the subjects investigated.

As the authors mention, given the modest modifying effect (i.e. +/− 1 to 5 ms) of most genetic loci/SNPs found to modulate the QTc duration in the general population, it is not unexpected that the isolated effect of these genetic loci on cardiac repolarization would be completely "washed out" by the predominant QTc-prolonging effect of the primary LQTS-causative mutation. However, statistical power arguments aside the failure to replicate the findings of previous studies, particularly the association of *NOS1AP* rs4657139 and rs16847548 with an increased risk of cardiac events, highlights the fact that genetic modifier studies in relatively rare disorders such as LQTS are often subject to unavoidable biases introduced by 1) the comparison of unrelated individuals with LQTS-causative mutations of variable strength from heterogeneous genetic backgrounds, 2) the isolated study of related individuals with the same LQTS-causative mutation from relatively homogenous genetic backgrounds, 3) the study of individual genetic variants in complete isolation, and/or 4) the use of variable methodological approaches that limit the generalization of results to LQTS individuals and populations not included in the initial study cohort(s).

That said, the novel approach employed by Guicheney et al to couple modifier discovery in a matched case-control cohort with subsequent replication in established founder populations represents an earnest attempt to eliminate or at least balance some of these unavoidable biases and certainly has the potential to advance the discovery of "modifier genes" in LQTS in the future. However, the precise clinical utility of this study's findings remains unknown and, as the authors acknowledge, will depend ultimately on elucidating the precise mechanism(s) by which *KCNQ1* rs2074238 is anti-arrhythmic in LQTS. Assuming that the *KCNQ1* rs2074238 SNP is not simply a tag SNP for an unknown protective mechanism buried within a larger haplotype block in tight linkage disequilibrium, the cited *in silico* evidence suggests that *KCNQ1* rs2074238 most likely exerts it modifying effect in an allele-specific fashion via the modulation of *KCNQ1* expression similar to recently described SNPs in the 3′ untranslated region (3′UTR) of *KCNQ1*.[18, 19] If this is indeed the case, the protective effect of *KCNQ1* rs2074238 might become even more pronounced once the genomic context between the SNP and LQTS-causative mutation (e.g. whether rs2074238 resides on the wild-type allele or the mutated *KCNQ1* allele) is accounted for properly.

While candidate-based approaches to modifier discovery have yielded a number of important genetic determinants of LQTS disease severity in recent years, including the discovery of modifying SNPs in *NOS1AP*[16,17], the 3′UTR of *KCNQ1*[19], and now the intronic *KCNQ1* rs2074238[18], the study of the effects of these SNPs in relative isolation (i.e. interaction of a single candidate SNP with a single LQTS-causative mutation) fails to take into account that the genome of each individual hosts a unique combination of common and rare genetic variants that could theoretically act in synergy or opposition to collectively modulate the phenotypic expression of a distinct primary LQTS-causative mutation. Furthermore, the genomic context of these modifying variants in relation to each other as well as to the primary LQTS-causative mutation adds an additional dimension to the already complex interplay between genetic and environmental determinants of LQTS disease severity. As one begins to ponder the various combinations of variants in transcriptional, translational, biosynthetic, and signaling pathways that could in theory modify cardiac ion channel function, it becomes apparent that the reductionistic, one-at-a-time candidate modifier approaches may need to be supplanted or at least complimented by unbiased genome-wide and systems biology approaches if we truly wish to understand the complex genetic architecture underlying congenital LQTS and begin to translate this knowledge in meaningful ways that might enhance how patients with this potentially lethal, yet highly

treatable genetic disorder are diagnosed, risk-stratified, and clinically managed in the post-genomic era.

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Table 1

Common variants previously shown to modify congenital LQTS disease severity and or QTc interval duration in health.

Locus (Nearest Gene)	SNP ID	MAF	Location (Amino Acid Change)	Function	Cohort(s)*	Previously Reported Effect	Effect on LQTS Phenotype¶
1q (*NOS1AP*)	rs12143842	0.16	Intergenic	Nitric oxide synthetase 1 adaptor protein	Health and LQTS	↑QTc	No Effect
	rs2880058	0.26	Intergenic		Health	↑QTc	Not Tested
	rs10494366	0.33	Intronic		Health and LQTS	↓QTc	No Effect
	rs12029454	0.11	Intronic		Health and LQTS	↑QTc	Deleterious
	rs16857031	0.15	Intronic		Health	↑QTc	No Effect
	rs4657139	0.18	Intronic		Health	↑QTc	No Effect
	rs4657178	0.26	Intergenic		Health	↑QTc	No Effect
1q (*ATP1B1*)	rs10919071	0.11	Intronic	Na/K ATPase β-subunit	Health	↑QTc	No Effect
1p (*RNF207*)	rs846111	0.26	Coding (G603A)	Ring finger protein	Health	↑QTc	Not Tested
3p (*SCN5A*)	rs11129795	0.34	Intergenic	Nav1.5 α-subunit (I_{Na})	Health	↓QTc	Not Tested
	rs12053903	0.29	Intronic		Health	↓QTc	No Effect
	rs1805124	0.18	Coding (H558R)		Health and LQTS	↑QTc	No Effect
4p (*ADRA2C*)	rs61767072	0.06	Coding (Δ322–325)	α2 adrenergic receptor	LQTS	↑Adrenergic response#	No Effect
6q (*c6orf204*)	rs11756438	0.47	Intergenic	Phospholamban	Health	↑QTc	No Effect
	rs12210810	0.08	Intergenic		Health	↓QTc	No Effect
7q (*KCNH2*)	rs4725982	0.18	Intergenic	Kv11.1 α-subunit (I_{Kr})	Health	↑QTc	Not Tested
	rs2968864	0.26	Intergenic		Health	↓QTc	Not Tested
	rs3778873	0.16	Intronic		Health	↓QTc	No Effect
	rs3807375	0.38	Intronic		Health	↑QTc	No Effect
	rs3815459	0.22	Intronic		Health	↓QTc	No Effect
	rs1805123	0.24	Coding (K897T)		Health and LQTS	Discordant	No Effect
10q (*ADRB1*)	rs1801252	0.22	Coding (S49G)	β1 adrenergic receptor	LQTS	↑Adrenergic response#	No Effect
	rs1801253	0.3	Coding (G389R)		LQTS	↑Adrenergic response#	No Effect
11p (*KCNQ1*)	rs2074238	0.08	Intronic	Kv7.1 α-subunit (I_{Ks})	Health and LQTS	↓QTc	Protective
	rs12576239	0.16	Intronic		Health	↑QTc	Not Tested

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Locus (Nearest Gene)	SNP ID	MAF	Location (Amino Acid Change)	Function	Cohort(s)*	Previously Reported Effect	Effect on LQTS Phenotype¶
	rs12296050	0.23	Intronic		Health	↑QTc	No Effect
	rs757092	0.35	Intronic		Health	↓QTc	No Effect
	rs2519184	0.09	3′ UTR		LQTS	Allele-specific	Not Tested
	rs8234	0.49	3′ UTR		LQTS	Allele-specific	Not Tested
	rs10798	0.49	3′ UTR		LQTS	Allele-specific	Not Tested
16p (*LITAF)*	rs8049607	0.49	Intergenic	Tumor necrosis factor	Health	↑QTc	Not Tested
16q (*CNOT1)*	rs37062	0.27	Intronic	RNA transcription	Health	↓QTc	Not Tested
17q (*KCNJ2)*	rs17779747	0.32	Intergenic	$K_{ir}2.1$ α-subunit (I_{K1})	Health	↓QTc	No Effect
17q (*LIG3)*	rs2074518	0.49	Intronic	DNA ligase III	Health	↓QTc	Not Tested
21q (*KCNE1)*	rs1805128	0.01	Coding (D85N)	MinK β-subunit (I_{Ks})	Health and LQTS	↑QTc	No Effect

*Health cohorts defined as QTSCD and or QTGEN genome-wide association studies[14,15]; LQTS cohort is used to define a multitude of studies in congenital LQTS summarized previously in Giudicessi et al.[4]

#Increased adrenergic response as assessed by higher baroreflex sensitivity values has associated with an increased risk of cardiac events in LQT1, but does not appear to be mediated by QTc interval.

¶Summary of the modifying effect observed in the study by Guicheney et al in the current edition of *Circulation: Cardiovascular Genetics*.[18]

Abbreviations: 3′UTR, 3′ untranslated region and LQTS, long-QT syndrome