SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLES

Table S1: List of Mutations by Coding Effect, Location, and Frequency in 406 LQT3 Patients. The different regions of the *SCN5A*-encoded Nav1.5 channel were defined as the coding sequence involving amino acid (aa) residues from N-terminus (aa1-126), DI (aa127-415), IDL I-II (aa416-711), DII (aa712-939), IDL II-III (aa940-1200), DIII (aa1201-1470), IDL III-IV (aa1471-1523), DIV (aa1524-1772) and C-terminus (aa1773-2016).

Coding Effect	Location	COUNT
V125L	N-term	1
Q245K	DI-S4/S5	3
R340W	DI-S4/S5	7
T370M	DI-S5/S6	9
N406K	DI-S6	1
V411M	DI-S6	7
A413T	DI-S6	3
L604V	DI/DII	2
G615E	DI/DII	2
P627L	DI/DII	2
Q692K	DI/DII	1
S941N	DII/DIII	1
R971C	DII/DIII	1
P1008S	DII/DIII	1
P1021S	DII/DIII	5
T1069M	DII/DIII	1
D1114E	DII/DIII	15
E1208K	DIII-S1	1
N1269S	DIII-S2/S3	6
I1278N	DIII-S3	5
T1304M	DIII-S4	9
N1325S	DIII-S4/S5	21
A1330D	DIII-S4/S5	1
A1330T	DIII-S4/S5	5
I1448L	DIII-S6	1
L1501V	DIII/DIV	13
K1505_Q1507del	DIII/DIV	9
Q1507_P1509del	DIII/DIV	55
L1560F	DIV-S2	1
F1596I	DIV-S3	5
F1617del	DIV-S3/S4	5
R1623L	DIV-S4	3

Coding Effect	Location	COUNT
R1623Q	DIV-S4	1
G1631D	DIV-S4	2
R1644H	DIV-S4	2
V1667I	DIV-S5	2
A1746T	DIV-S6	4
I1762del	DIV-S6	1
V1763M	DIV-S6	2
M1766L	DIV-S6	1
M1766V	DIV-S6	10
Y1767C	DIV-S6	4
I1768V	DIV-S6	58
V1777M	Cterm	2
T1779M	C-term	5
E1781G	C-term	3
E1784K	C-term	70
L1786Q	C-term	3
D1790G	C-term	30
Y1795C	C-term	3
R1991Q	C-term	1
TOTAL		**406**

Supplemental Table S2. LQT3 subjects with events before age 1 or no follow-up after Age 1.

Center	Gender	QTc (ms)	Syncope (Age)	ACA (Age)	Sudden Cardiac Death (Age)	Coding Effect	Mutation Location
Denmark	Male	No ECG	No	No	No	R340W	IS5-IS6
Mayo Clinic	Female	460	Yes (0)	No	No	N406K	IS6
Italy	Male	442	No	No	No	A413T	IS6
Italy	Male	550	No	Yes (0)	Yes (4)	S941N	IIS6-IIIS1
Rochester	Male	380	Yes (0)	No	No	T1304M	IIIS4
Italy	Male	520	Yes (0)	Yes (0)	Yes (0)	A1330D	IIIS4-IIIS5
Rochester	Female	440	Yes (0)	No	No	Q1507-P1509del	IIIS6-IVS1
Rochester	Female	590	Yes (0)	Yes (0)	No	R1623Q	IVS4
Italy	Male	520	No	Yes (0)	No	G1631D	IVS4
Japan	Male	550	Yes (0)	Yes (0)	No	G1631D	IVS4
Italy	Male	No ECG	No	Yes (0)	Yes (0)	V1763M	IVS6
Mayo Clinic	Male	490	No	Yes (1.5)	Yes (1.5)	M1766L	DIV-S6
Netherlands	Female	420	No	No	No	I1768V	IVS6
Rochester	Female	510	Yes (0)	No	No	E1784K	C-TERM
Israel	Male	470	No	No	Yes (0)	D1790G	C-TERM

Supplemental Table S3. Numbers of Subjects and Events by Time-Dependent ß-Blocker Status (BB).

	No CE (no ACA/SCD)	1st CE on BB (1st ACA/SCD on BB)	1st CE off BB (1st ACA/SCD off BB)	Total
All Patients				
Never on BB during follow-up to 1st CE (1st ACA/SCD)	205 (241)	0 (0)	107 (49)	312 (290)
Ever on BB during follow-up to 1st CE (1st ACA/SCD)	69 (95)	9 (5)	2 (2)	80 (102)
Total # Subjects	274 (336)	9 (5)	109 (51)	392 (392)
Males				
Never on BB during follow-up to 1st CE (1st ACA/SCD)	100 (112)	0 (0)	32 (14)	132 (126)
Ever on BB during follow-up to 1st CE (1st ACA/SCD)	33 (45)	7 (3)	2 (0)	43 (48)
Total # Male Subjects	133 (157)	7 (3)	34 (14)	174 (174)
Females				
Never on BB during follow-up to 1st CE (1st ACA/SCD)	105 (129)	0 (0)	75 (35)	180 (164)
Ever on BB during follow-up to 1st CE (1st ACA/SCD)	36 (50)	2 (2)	0 (2)	38 (54)
Total # Female Subjects	141 (179)	2 (2)	75 (37)	218 (218)

Note: numbers not in parentheses refer to cardiac events (CE) including syncope, aborted cardiac arrest (ACA), or sudden cardiac death (SCD) whichever came first as categorized as No CE, 1st CE on BB, and 1st CE off BB. Numbers in parentheses refer to ACA or SCD whichever occurred first as categorized as No ACA/SCD, 1st ACA/SCD on BB, and 1st ACA/SCD off BB. This table provides rough background information on numbers of patients in the time-dependent ß-blocker Cox multivariate analyses by gender. See Table 2 in the main manuscript for specific hazard ratios, confidence intervals, and p-values.

Supplemental Comment Regarding Interpretation of the Cox Model and the Derived Figures 4A and 4B.

This was a focused, pre-specified analysis with only a small number of candidate predictors, all of which were included in the final Cox models, irrespective of statistical significance.

In Cox analyses, if properly specified, adjusting for QTc, birth year, gender, mutation and time-dependent syncope means that comparisons between patients on versus off beta-blockers are only made between matched subgroups of patients with identical QTc values, birth year, age (since age is the time scale), gender, mutation, and syncopal history. For example, female patients with the I1768V mutation and a QTc of 470 ms who were born in 1971 who are asymptomatic and *on* ß-blockers at age 29 are effectively matched and compared to female patients with the I1768V mutation and a QTc of 470 ms who were born in 1971 who are asymptomatic and *off* ß-blockers at age 29. This is what is meant by the covariate-adjusted hazard ratio for beta-blockers. Thus, one need not be concerned with any potential differences -- at baseline or at any other point during follow-up -- in QTc, birth year, gender, mutation, or syncopal history when the model is properly specified.

The figures shown here are not Kaplan-Meier curves, but rather predicted event rates. Each male contributes information to both "always on" and "never on" ß-blocker curves, as does each female. Furthermore, predicted event rates depend strongly on all significant risk factors in the Cox model (Table 2). As shown in Figure 4B, QTc $\geq$ 500 ms approximately doubles the 40-year event rates to >70% for females never on BB and about 25% for others. Prior syncope, especially at a young age, would further increase the event rates. On the other hand, 40-year event rates for those with the lower risk D1790G mutation are < 5% for most subjects and < 15% even for females never on ß-blockers, while event rates are even lower among those with the E1784K mutation.

An example on how these curves can be used and interpreted is provided in the following description: the absolute risk predicted by the model for an asymptomatic woman age 25 in the medium risk profile group off ß-blockers (figure 4a) is ±20% and in the high-risk group ±40% (figure 4b). ß-blocker therapy would reduce that risk to ±5% and ±10% in the medium- and high-risk groups, respectively.