Supplemental Material

Common Genetic Variants Explain Variability in Drug-Induced QT Prolongation

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Supplementary Table 1: Common genetic variants for QT score

SNP	Chr.	Nearest Gene	QT Raising Allele	European genetic QT score weight	African American genetic QT score weight	0 copies (%)	1 copy (%)	2 copies (%)	Missing (%)
rs10919070	1	ATP1B1	A	1.668	-2.063	0	13.6	86.4	0
rs11809180	1	ATP1B1	C	1.163	-1.574	0	18.2	77.3	4.5
rs12061601	1	ATP1B1	T	1.38	-1.888	9.1	13.6	72.7	4.5
rs1983546	1	ATP1B1	A	0.8174	-0.6946	36.4	31.8	31.8	0
rs545833	1	ATP1B1	T	0.8518	0.4236	59.1	18.2	18.2	4.5
rs12025136	1	NOS1AP	C	1.449	0.0336	50	18.2	27.3	4.5
rs12143842	1	NOS1AP	T	3.489	3.144	50	31.8	0	18.2
rs164133	1	NOS1AP	C	0.706	-0.2965	50	40.9	4.5	4.5
rs16857031	1	NOS1AP	G	2.365	0.7958	68.2	9.1	4.5	18.2
rs17460657	1	NOS1AP	A	4.997	0.3507	0	13.6	81.8	4.5
rs347272	1	NOS1AP	A	1.804	-0.3486	59.1	22.7	0	18.2
rs3934467	1	NOS1AP	T	2.759	1.688	59.1	22.7	0	18.2
rs4656345	1	NOS1AP	G	4.845	-4.709	4.5	0	86.4	9.1
rs2273042	1	RNF207	A	0.9223	-0.6483	77.3	13.6	0	9.1
rs846111	1	RNF207	C	1.69	0.6535	59.1	27.3	0	13.6
rs2298632	1	TCEA3	T	0.7924	0.6809	45.5	31.8	18.2	4.5
rs12997023	2	SLC8A1	T	1.694	-1.675	4.5	4.5	77.3	13.6
rs6544311	2	SLC8A1	A	0.6505	-0.9235	50	40.9	9.1	0
rs938291	2	SP3	G	0.5482	0.3565	27.3	36.4	13.6	22.7
rs295140	2	SPATS2L	T	0.5534	0.358	31.8	40.9	13.6	13.6
rs7561149	2	TTN-CCDC141	T	0.5287	-0.3299	18.2	22.7	45.5	13.6
rs17784882	3	C3ORF75	C	0.5342	0.1658	13.6	22.7	54.5	9.1
rs11708996	3	SCN5A-SCN10A	G	0.9123	-2.919	0	18.2	77.3	4.5
rs6793245	3	SCN5A-SCN10A	G	1.107	-0.5121	13.6	27.3	45.5	13.6
rs6801957	3	SCN5A-SCN10A	C	0.6181	-0.9547	4.5	31.8	50	13.6
rs9851710	3	SCN5A-SCN10A	C	0.6628	0.1167	45.5	31.8	9.1	13.6
rs2363719	4	SLC4A4	A	0.9567	-0.5002	86.4	9.1	0	4.5
rs3857067	4	SMARCAD1	T	0.5091	-0.1312	18.2	31.8	27.3	22.7
rs10040989	5	GFRA3	G	0.8571	0.0051	4.5	9.1	86.4	0
rs7765828	6	GMPR	G	0.6208	-0.0931	40.9	27.3	27.3	4.5
rs10499087	6	SLC35F1-PLN	C	0.7001	0.1828	72.7	9.1	4.5	13.6
rs11153730	6	SLC35F1-PLN	C	1.647	-0.565	40.9	9.1	45.5	4.5

rs12210733	6	SLC35F1-PLN	G	2.036	0.6448	0	4.5	95.5	0
rs17349133	6	SLC35F1-PLN	C	0.857	-0.4496	0	36.4	54.5	9.1
rs465226	6	SLC35F1-PLN	T	1.844	0.1849	0	0	100	0
rs9920	7	CAV1	C	0.8447	-0.1587	63.6	4.5	0	31.8
rs1805121	7	KCNH2	C	1.278	NA	22.7	40.9	36.4	0
rs2072413	7	KCNH2	C	1.673	-1.343	9.1	36.4	40.9	13.6
rs1961102	8	AZIN1	T	0.5836	0.3118	59.1	18.2	13.6	9.1
rs16936870	8	NCOA2	A	0.9739	0.6432	77.3	18.2	4.5	0
rs2485376	10	GBF1	G	0.5629	-0.0445	22.7	36.4	36.4	4.5
rs174583	11	FADS2	C	0.6575	-0.6151	4.5	27.3	54.5	13.6
rs2074238	11	KCNQ1	C	4.94	-3.112	0	9.1	90.9	0
rs7122937	11	KCNQ1	T	1.928	1.347	45.5	18.2	31.8	4.5
rs3026445	12	ATP2A2	C	0.5717	0.474	40.9	36.4	13.6	9.1
rs728926	13	KLF12	T	0.5746	0.3524	45.5	22.7	27.3	4.5
rs2273905	14	ANKRD9	T	0.6938	1.096	59.1	27.3	13.6	0
rs3105593	15	USP50-TRPM7	T	0.67	0.9802	54.5	31.8	13.6	0
rs246258	16	CNOT1	C	1.732	-1.392	0	31.8	50	18.2
rs4784934	16	CNOT1	A	0.6815	0.3654	63.6	18.2	9.1	9.1
rs1296720	16	CREBBP	C	0.834	0.5728	81.8	4.5	9.1	4.5
rs12444261	16	LITAF	G	0.7988	-0.888	4.5	22.7	68.2	4.5
rs735951	16	LITAF	G	1.156	-1.436	27.3	36.4	22.7	13.6
rs246185	16	MKL2	C	0.7205	0.373	50	27.3	13.6	9.1
rs10775360	17	KCNJ2	C	0.7672	-0.2469	22.7	13.6	50	13.6
rs1396515	17	KCNJ2	G	0.9762	-0.4522	13.6	13.6	54.5	18.2
rs17763769	17	KCNJ2	A	0.8944	-0.5354	77.3	13.6	4.5	4.5
rs236586	17	KCNJ2	G	0.6408	1.002	45.5	36.4	13.6	4.5
rs1052536	17	LIG3	C	0.9715	0.8081	22.7	22.7	27.3	27.3
rs9892651	17	PRKCA	T	0.7387	-0.7171	31.8	27.3	22.7	18.2
rs1805128	21	KCNE1	T	1.014	14.18	100	0	0	0

Supplementary Table 2: Baseline QTc vs. drug slope response by race

Group	*r* [95% CI]	*P*	*N*	r^2
All Subjects				
Baseline QTc vs. Dofetilide QTc slope	0.45 [0.03 to 0.73]	0.04	22	0.20
Baseline QTc vs. Quinidine QTc slope	<0.01 [-0.46 to 0.40]	0.89	21	<0.01
Baseline QTc vs. Ranolazine QTc slope	0.18 [-0.26 to 0.56]	0.43	22	0.03
White				
Baseline QTc vs. Dofetilide QTc slope	0.38 [-0.13 to 0.73]	0.14	17	0.14
Baseline QTc vs. Quinidine QTc slope	<0.01 [-0.53 to 0.46]	0.86	16	<0.01
Baseline QTc vs. Ranolazine QTc slope	0.03 [-0.46 to 0.50]	0.92	17	<0.01
Black				
Baseline QTc vs. Dofetilide QTc slope	0.96 [-0.02 to 1.00]	0.04	4	0.92
Baseline QTc vs. Quinidine QTc slope	0.42 [-0.91 to 0.98]	0.58	4	0.17
Baseline QTc vs. Ranolazine QTc slope	0.64 [-0.83 to 0.99]	0.36	4	0.41

Asian group not reported because only 1 subject was Asian. Supplementary Figure I shows the corresponding correlation plots.

Supplementary Table 3. Correlations between common genetic variant QT score and drug-induced T_{peak}-T_{end} slope response

Genetic QT score vs. treatment (white subjects)	***r* [95% CI]**	***P***	***N***	r^2
Genetic score vs. Baseline T_{peak}-T_{end}	0.27 [-0.24 to 0.67]	0.29	17	0.07
Genetic score vs. Dofetilide T_{peak}-T_{end} slope	0.13 [-0.37 to 0.58]	0.61	17	0.02
Genetic score vs. Quinidine T_{peak}-T_{end} slope	0.27 [-0.26 to 0.68]	0.31	16	0.07
Genetic score vs. Ranolazine T_{peak}-T_{end} slope	0.38 [-0.12 to 0.73]	0.13	17	0.14
Genetic QT score vs. treatment (black or African American subjects)	***r* [95% CI]**	***P***	***N***	r^2
Genetic score vs. Baseline T_{peak}-T_{end}	0.87 [-0.56 to 1.00]	0.13	4	0.76
Genetic score vs. Dofetilide T_{peak}-T_{end}	0.86 [-0.58 to 1.00]	0.14	4	0.74
Genetic score vs. Quinidine T_{peak}-T_{end} slope	<0.01 [-0.99 to 0.86]	0.41	4	0.35
Genetic score vs. Ranolazine T_{peak}-T_{end} slope	0.94 [-0.24 to 1.00]	0.06	4	0.88

Supplementary Table 4: Baseline T_{peak}-T_{end} vs. drug QTc slope response by race

Group	*r* [95% CI]	*P*	*N*	r^2
All Subjects				
Baseline T_{peak}-T_{end} vs. Dofetilide QTc slope	0.59 [0.23 to 0.81]	<0.01	22	0.35
Baseline T_{peak}-T_{end} vs. Quinidine QTc slope	0.78 [0.52 to 0.91]	<0.001	21	0.61
Baseline T_{peak}-T_{end} vs. Ranolazine QTc slope	0.37 [-0.06 to 0.69]	0.09	22	0.14
White				
Baseline T_{peak}-T_{end} vs. Dofetilide QTc slope	0.65 [0.24 to 0.86]	<0.01	17	0.42
Baseline T_{peak}-T_{end} vs. Quinidine QTc slope	0.80 [0.50 to 0.93]	<0.001	16	0.64
Baseline T_{peak}-T_{end} vs. Ranolazine QTc slope	0.41 [-0.09 to 0.74]	0.11	17	0.17
Black				
Baseline T_{peak}-T_{end} vs. Dofetilide QTc slope	0.96[-0.07 to 1.00]	0.05	4	0.91
Baseline T_{peak}-T_{end} vs. Quinidine QTc slope	0.17 [-0.95 to 0.97]	0.83	4	0.03
Baseline T_{peak}-T_{end} vs. Ranolazine QTc slope	0.11 [-0.95 to 0.97]	0.89	4	0.01

Asian group not reported because only 1 subject was Asian.

Supplementary Table 5: Baseline T_{peak}-T_{end} vs. drug T_{peak}-T_{end} slope response by race

Group	*r* [95% CI]	*P*	*N*	r^2
All Subjects				
Baseline T_{peak}-T_{end} vs. Dofetilide T_{peak}-T_{end} slope	0.72 [0.43 to 0.88]	<0.001	22	0.52
Baseline T_{peak}-T_{end} vs. Quinidine T_{peak}-T_{end} slope	0.66 [0.33 to 0.85]	<0.01	21	0.44
Baseline T_{peak}-T_{end} vs. Ranolazine T_{peak}-T_{end} slope	0.50 [0.10 to 0.76]	0.02	22	0.25
White				
Baseline T_{peak}-T_{end} vs. Dofetilide T_{peak}-T_{end} slope	0.69 [0.31 to 0.88]	<0.01	17	0.47
Baseline T_{peak}-T_{end} vs. Quinidine T_{peak}-T_{end} slope	0.69 [0.30 to 0.89]	<0.01	16	0.48
Baseline T_{peak}-T_{end} vs. Ranolazine T_{peak}-T_{end} slope	0.40 [-0.10 to 0.74]	0.12	17	0.16
Black				
Baseline T_{peak}-T_{end} vs. Dofetilide T_{peak}-T_{end} slope	1.00[0.88 to 1.00]	0<0.01	4	0.99
Baseline T_{peak}-T_{end} vs. Quinidine T_{peak}-T_{end} slope	<0.01 [-0.98 to 0.92]	0.65	4	0.13
Baseline T_{peak}-T_{end} vs. Ranolazine T_{peak}-T_{end} slope	0.89 [-0.50 to 1.00]	0.11	4	0.79

Asian group not reported because only 1 subject was Asian.

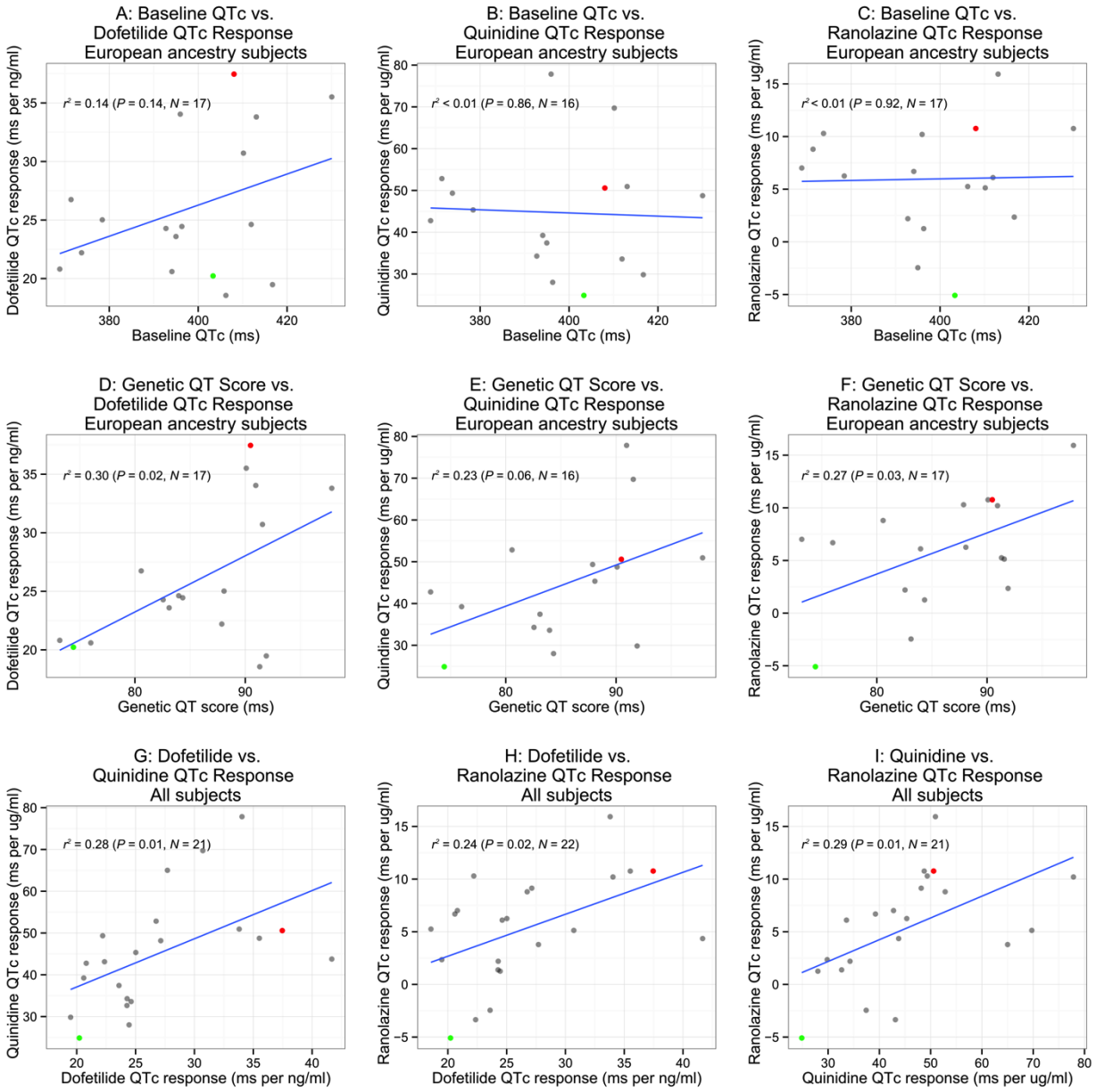
Supplementary Table 6. Association results for individual torsade de pointes variants from the QT interval score. Variants with imputation quality scores > 0.9 were included in the QT score analysis.

SNP	CHR	position (hg19)	coded allele	coded allele freq	effect (ln(OR))	SE	P	imputed	imputation quality
rs2273042	1	6149122	A	0.12	-0.22	0.19	0.256	0	1.00
rs846111	1	6279370	C	0.19	-0.18	0.22	0.422	1	0.76
rs2298632	1	23710475	C	0.49	-0.12	0.12	0.289	0	1.00
rs6669543	1	161981025	T	0.24	-0.07	0.14	0.608	1	0.94
rs4656345	1	161991237	NA	NA	NA	NA	NA	NA	NA
rs12143842	1	162033890	T	0.27	0.30	0.13	0.020	0	0.98
rs16857031	1	162112910	G	0.15	0.11	0.16	0.493	1	0.58
rs17457880	1	162168154	A	0.01	-0.62	0.58	0.288	1	1.00
rs4657172	1	162179632	C	0.11	-0.24	0.20	0.231	1	0.99
rs3934467	1	162182677	T	0.22	0.12	0.14	0.390	1	0.99
rs7545047	1	162191103	A	0.05	-0.11	0.28	0.684	1	0.59
rs17460657	1	162261826	C	0.02	0.41	0.42	0.331	1	0.99
rs347272	1	162318498	A	0.14	0.41	0.17	0.015	1	1.00
rs164133	1	162381288	C	0.27	-0.11	0.13	0.418	1	1.00
rs545833	1	168689940	T	0.28	0.28	0.13	0.039	0	1.00
rs12061601	1	169070450	C	0.11	-0.23	0.20	0.242	0	1.00
rs10919070	1	169099037	C	0.13	-0.28	0.19	0.143	1	0.99
rs12079745	1	169101060	A	0.05	-0.20	0.28	0.471	1	1.00
rs1983546	1	169446183	G	0.35	-0.13	0.12	0.289	0	0.99
rs6544311	2	40353277	A	0.39	0.37	0.13	0.003	1	1.00
rs12997023	2	40752982	C	0.04	-0.21	0.33	0.525	1	0.99
rs938291	2	174742608	G	0.38	-0.05	0.12	0.671	1	1.00
rs7561149	2	179689856	C	0.40	-0.07	0.12	0.551	1	1.00
rs295140	2	201160699	T	0.43	0.07	0.12	0.552	0	0.99
rs6793245	3	38599037	A	0.31	-0.20	0.13	0.134	1	1.00
rs11708996	3	38633923	C	0.14	0.02	0.17	0.884	1	0.94
rs11710077	3	38657899	T	0.20	0.44	0.15	0.004	1	0.98
rs6599234	3	38715300	A	0.30	0.03	0.13	0.801	1	1.00
rs6801957	3	38767315	T	0.41	0.08	0.12	0.525	1	1.00
rs17784882	3	47544003	A	0.41	0.08	0.12	0.504	0	1.00
rs2363719	4	72138216	A	0.11	0.10	0.19	0.581	0	1.00
rs3857067	4	95026434	A	0.49	-0.05	0.12	0.670	1	1.00
rs10040989	5	137573725	A	0.13	-0.21	0.19	0.275	0	0.95
rs7765828	6	16294722	G	0.37	0.06	0.13	0.624	1	1.00
rs457162	6	118535983	T	0.05	0.62	0.25	0.012	1	1.00
rs12210733	6	118653075	A	0.06	0.07	0.25	0.775	1	1.00
rs11153730	6	118667522	C	0.49	0.25	0.12	0.038	1	1.00

rs3902035	6	119000232	C	0.32	0.03	0.12	0.835	1	1.00
rs9489510	6	119043898	G	0.32	0.18	0.13	0.172	0	1.00
rs9920	7	116200092	C	0.10	-0.03	0.20	0.885	0	1.00
rs2072413	7	150647969	NA	NA	NA	NA	NA	NA	NA
rs3807375	7	150667210	T	0.37	0.08	0.12	0.495	1	0.99
rs16936870	8	71189342	A	0.10	0.12	0.20	0.552	1	1.00
rs11779860	8	98850330	C	0.46	-0.06	0.12	0.624	0	1.00
rs1961102	8	103932845	T	0.35	0.08	0.12	0.537	1	0.52
rs2485376	10	104050006	A	0.37	-0.05	0.13	0.674	1	0.82
rs2301696	11	2426984	C	0.47	0.02	0.26	0.930	1	0.98
rs2074238	11	2484803	T	0.06	-0.24	0.29	0.403	1	0.98
rs7122937	11	2486550	T	0.19	0.33	0.15	0.026	1	1.00
rs174583	11	61609750	T	0.36	-0.03	0.12	0.804	0	1.00
rs3026445	12	110723203	C	0.36	0.07	0.13	0.550	0	0.98
rs728926	13	74513122	T	0.39	0.11	0.12	0.384	1	1.00
rs2273905	14	102974999	T	0.35	0.05	0.12	0.655	0	1.00
rs3105593	15	50845018	T	0.47	0.04	0.12	0.736	0	0.95
rs1296720	16	3873642	C	0.21	0.12	0.15	0.402	1	1.00
rs12930096	16	11670758	T	0.17	-0.14	0.16	0.379	0	0.95
rs735951	16	11693536	A	0.46	-0.19	0.12	0.114	1	0.96
rs12444261	16	11734642	T	0.24	0.02	0.15	0.872	1	0.99
rs246185	16	14395432	C	0.32	0.06	0.13	0.662	1	1.00
rs4784934	16	58459926	A	0.28	0.13	0.13	0.311	1	1.00
rs246196	16	58574253	C	0.26	0.01	0.14	0.954	1	1.00
rs1052536	17	33331575	T	0.48	-0.19	0.12	0.125	0	0.99
rs9892651	17	64303793	C	0.42	0.15	0.12	0.199	1	1.00
rs236586	17	68203546	G	0.48	0.15	0.12	0.219	1	1.00
rs10775360	17	68325868	T	0.29	-0.22	0.13	0.091	1	1.00
rs1396515	17	68430993	G	0.48	-0.05	0.12	0.679	0	1.00
rs17763769	17	68560789	A	0.14	0.04	0.17	0.822	0	1.00
rs1805128	21	35821680	NA	NA	NA	NA	NA	NA	NA

Supplementary Table 7. Effects on QTc slope of genetic QT score using 61 SNPs at 31 loci (full) and restricted to 1 SNP per locus (index only)

		Genetic QT score (white subjects)			
		Full		*Index only*	
Treatment	***N***	***P***	***r^2***	***P***	***r^2***
Baseline QTc	*17*	*0.03*	*0.27*	*0.10*	*0.17*
Dofetilide QTc slope	*17*	*0.02*	*0.30*	*0.19*	*0.11*
Quinidine QTc slope	*16*	*0.06*	*0.23*	*0.45*	*0.04*
Ranolazine QTc slope	*17*	*0.03*	*0.27*	*0.42*	*0.04*



Supplementary Figure 1: Correlations between baseline QTc and QTc slope, genetic score and QTc slope as well as QTc slope between drugs. Correlation between baseline QTc and QTc slope of dofetilide (A), quinidine (B) and ranolazine (C) in white subjects. Correlation between European ancestry genetic QT score and QTc slope of dofetilide (D), quinidine (E) and ranolazine (F) in white subjects. Correlation between dofetilide and quinidine QTc slopes (G), dofetilide and ranolazine QTc slope (H) and quinidine and ranolazine QTc slopes (I). All correlations computed in white subjects. Each dot corresponds with a subject. Example subjects are shown in red (dofetilide high responder) and green (low responder).

Supplementary Figure 2. Sensitivity analysis of genotype score in cases of drug-induced torsade de pointes. Instrumental variable analysis of effect of 31 SNPs associated with resting QTc (restricted to only one SNP per locus), using effect estimates from the QT-IGC GWA study (x axis) in milliseconds of QT interval per allele as a predictor of log odds ratio of diTdP (y axis). Individual labels represent SNPs used in the analysis, and error bars correspond to the standard error of the log odds ratio of drug-induced torsade de pointes.