Figure legends

Figure 1. Generation and characterisation of a LQTS2-hiPSC line. Panel (A) shows the electrocardiogram of the LQTS2 patient during rest, with QTc of up to 571ms (Ai), and during an arrhythmic episode (Aii). After harvesting skin samples from the patient and using Sendai-based reprogramming, the resulting hiPSC line was shown to express markers of pluripotency by immunostaining (B) and flow cytometry (C). The LQTS2 hiPSCs showed a normal karyotype (D) and was heterozygote for the G/A mutation at nucleotide position 1681 in the *KCNH2* gene (E). Directed monolayer differentiation produced hiPSC-CMs of >80% purity (F). Optical recordings using the voltage-sensitive dye, FluoVolt, were made on the CellOPTIQ platform and showed that the action potential duration of LQTS2-hiPSC-CMs (red trace) was prolonged relative to hiPSC-CMs derived from her healthy father (black trace; G). In panel (H), LQTS2-hiPSC-CMs were assessed at baseline and after treatment with a 10-1000nM concentration range of the non-specific β-blocker, propranolol, which shows marginal impact on action potential duration. Data are mean±SEM with 40 replicates for BL (0) and 8 replicates for all other treatments; Dunnett's test; * P≤0.05. Scale bars = 100µm.

Figure 2. Direct modulation of I_{Kr} channels. LQTS2-hiPSC-CMs were treated with the plant constituent, Ginsenoside RG3, or the synthetic compound, NS1643. After loading with the voltage-sensitive dye, FluoVolt, optical recordings made using the CellOPTIQ platform. Averaged traces across the concentration range are shown in (A), while the derived percentage changes in APD_{50}, APD_{90} and triangularisation are shown in (Bi; RG3) and (Bii; NS1643). Data are mean±SEM with 40 replicates for BL (0) and 8 replicates for all other treatments; Dunnett's test comparison to baseline (BL [0]); * P≤0.05; ** P≤0.01; *** P≤0.001; **** P≤0.0001.

Figure 3. Indirect modulation of I_{Kr} channels with PPARδ agonists. LQTS2-hiPSC-CMs were treated with the PPARδ agonists, GW0742 and telmisartan, which are thought to stabilise the PKA-phosphorylated state of HERG via protein 14-3-3 epsilon. After loading with the voltage-sensitive dye, FluoVolt, optical recordings made using the CellOPTIQ platform. Averaged traces across the concentration range are shown in (A), while the derived percentage changes in APD_{50}, APD_{90} and triangularisation are shown in (Bi; GW0742) and (Bii; telmisartan). Data are mean±SEM with 40 replicates for BL (0) and 8 replicates for all other treatments; Dunnett's test comparison to baseline (BL [0]); * P≤0.05; ** P≤0.01; *** P≤0.001; **** P≤0.0001.

Figure 4. Modulation of I_{KATP}. LQTS2-hiPSC-CMs were treated with the I_{KATP} enhancers, minoxidil and nicorandil. After loading with the voltage-sensitive dye, FluoVolt, optical recordings made using the CellOPTIQ platform. Averaged traces across the concentration range are shown in (A), while the derived percentage changes in APD_{50}, APD_{90} and triangularisation are shown in (Bi; minoxidil) and (Bii; nicorandil). Data are mean±SEM with 40 replicates for BL (0) and 8 replicates for all other treatments; Dunnett's test comparison to baseline (BL [0]); * P≤0.05; ** P≤0.01; *** P≤0.001; **** P≤0.0001.