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**Calcium Transients Closely Reflect Prolonged Action Potentials in iPSC Models of Inherited Cardiac Arrhythmia.**

**Journal:** Stem Cell Reports

**Publication Year:** 2014

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**PubMed link:** 25254341

**Funding Grants:** Induced Pluripotent Stem Cells for Cardiovascular Diagnostics, Gladstone CIRM Scholars Program

**Public Summary:**

Long-QT syndrome mutations can cause syncope and sudden death by prolonging the cardiac action potential (AP). Ion channels affected by mutations are various, and the influences of cellular calcium cycling on LQTS cardiac events are unknown. To better understand LQTS arrhythmias, we performed current-clamp and intracellular calcium ( $[Ca^{2+}]_i$ ) measurements on cardiomyocytes differentiated from patient-derived induced pluripotent stem cells (iPS-CM). In myocytes carrying an LQT2 mutation (HERG-A422T), APs and  $[Ca^{2+}]_i$  transients were prolonged in parallel. APs were abbreviated by nifedipine exposure and further lengthened upon releasing intracellularly stored  $Ca^{2+}$ . Validating this model, control iPS-CM treated with HERG-blocking drugs recapitulated the LQT2 phenotype. In LQT3 iPS-CM, expressing NaV1.5-N406K, APs and  $[Ca^{2+}]_i$  transients were markedly prolonged. AP prolongation was sensitive to tetrodotoxin and to inhibiting  $Na^+-Ca^{2+}$  exchange. These results suggest that LQTS mutations act partly on cytosolic  $Ca^{2+}$  cycling, potentially providing a basis for functionally targeted interventions regardless of the specific mutation site.

**Scientific Abstract:**

Long-QT syndrome mutations can cause syncope and sudden death by prolonging the cardiac action potential (AP). Ion channels affected by mutations are various, and the influences of cellular calcium cycling on LQTS cardiac events are unknown. To better understand LQTS arrhythmias, we performed current-clamp and intracellular calcium ( $[Ca^{2+}]_i$ ) measurements on cardiomyocytes differentiated from patient-derived induced pluripotent stem cells (iPS-CM). In myocytes carrying an LQT2 mutation (HERG-A422T), APs and  $[Ca^{2+}]_i$  transients were prolonged in parallel. APs were abbreviated by nifedipine exposure and further lengthened upon releasing intracellularly stored  $Ca^{2+}$ . Validating this model, control iPS-CM treated with HERG-blocking drugs recapitulated the LQT2 phenotype. In LQT3 iPS-CM, expressing NaV1.5-N406K, APs and  $[Ca^{2+}]_i$  transients were markedly prolonged. AP prolongation was sensitive to tetrodotoxin and to inhibiting  $Na^+-Ca^{2+}$  exchange. These results suggest that LQTS mutations act partly on cytosolic  $Ca^{2+}$  cycling, potentially providing a basis for functionally targeted interventions regardless of the specific mutation site.

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