High throughput screening in silico via computer models of induced-pluripotent stem cell derived cardiomyocytes

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There is a profound need to develop a strategy to predict patient-to-patient vulnerability in the emergence of cardiac arrhythmia. A promising in vitro method to address patient-specific proclivity to cardiac disease utilizes induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). A major strength of this approach is that iPSC-CMs contain donor genetic information and therefore capture patient-specific genotype-phenotype relationships. A cited detriment of iPSC-CMs is the cell-to-cell variability observed in electrical activity. We postulated, however, that cell-to-cell variability may constitute a strength when appropriately utilized in a computational framework to build in silico cell populations that can be employed to identify phenotypic mechanisms and pinpoint key sensitive parameters. Thus, we have exploited variation in experimental data across multiple laboratories to develop a computational framework to investigate subcellular phenotypic mechanisms in healthy iPSC-CMs. In subsequent studies, this computational framework was utilized to explore genotype-phenotype relationships in control and diseased cases.