Modeling of *LMNA*-Related Dilated Cardiomyopathy Using Human Induced Pluripotent Stem Cells.

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**Abstract**

Dilated cardiomyopathy (DCM) is one of the leading causes of heart failure and heart transplantation. A portion of familial DCM is due to mutations in the *LMNA* gene encoding the nuclear lamina proteins lamin A and C and without adequate treatment these patients have a poor prognosis. To get better insights into pathobiology behind this disease, we focused on modeling *LMNA*-related DCM using human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM). Primary skin fibroblasts from DCM patients carrying the most prevalent Finnish founder mutation (p.S143P) in *LMNA* were reprogrammed into hiPSCs and further differentiated into cardiomyocytes (CMs). The cellular structure, functionality as well as gene and protein expression were assessed in detail. While mutant hiPSC-CMs presented virtually normal sarcomere structure under normoxia, dramatic sarcomere damage and an increased sensitivity to cellular stress was observed after hypoxia. A detailed electrophysiological evaluation revealed bradyarrhythmia and increased occurrence of arrhythmias in mutant hiPSC-CMs on β-adrenergic stimulation. Mutant hiPSC-CMs also showed increased sensitivity to hypoxia on microelectrode array and altered Ca<sup>2+</sup> dynamics. Taken together, p.S143P hiPSC-CM model mimics hallmarks of *LMNA*-related DCM and provides a useful tool to study the underlying cellular mechanisms of accelerated cardiac degeneration in this disease.

**KEYWORDS**: LMNA; Lamin A/C; dilated cardiomyopathy; hypoxia; induced pluripotent stem cell; microelectrode array and calcium imaging

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