Modeling Laminopathy-Driven Cardiac Dysfunction Under Microphysiological Conditions:

Insights from LMNA L35P Mutant hiPSC-Derived Cardiomyocytes

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Abstract

- Laminopathies are rare genetic disorders caused by mutations in the LMNA gene, presenting a broad range of symptoms such as Muscular Dystrophies, Lipodystrophies and Cardiomyopathies

- Cardiac manifestations, including arrhythmias, conduction defects, and contractile dysfunction are a leading cause of morbidity and mortality in these patients

- The underlying mechanisms by which LMNA mutations lead to cardiac dysfunction are still not fully understood, highlighting the need for better human-relevant disease models

- To address this, we used a high-throughput microphysiological system (FLEXcyte 96) to study contractility in a human induced pluripotent stem cell (iPSC)-derived cardiac cell line (iCell cardiomyocyte DCM, LMNA L35P, Fujifilm Cellular Dynamics) carrying the pathogenic LMNA L35P mutation, compared to its isogenic control

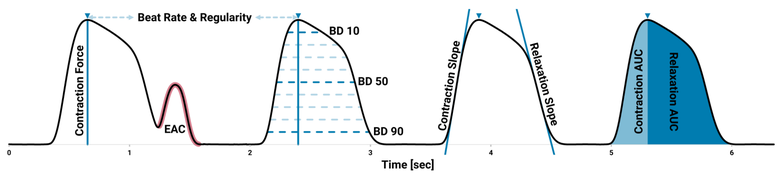
Methods

- Human L35P mutant and corrected iPSC-cardiomyocytes (hiPSC-CMs) were precultured for six days in special 96-well (FLEXcyte) plates, containing a flexible PDMS membrane as substrate for the cells to mimic in vivo-like heart conditions

- Functional measurements were assessed frequently in the FLEXcyte 96 system (Nanion Technologies) to test for contractile differences between the diseased and isogenic corrected cell line

- Contractile parameters tested were contraction force (mN/mm^2), beat rate, beat duration and arrhythmias

Figure 1



Results

Figure 2.A

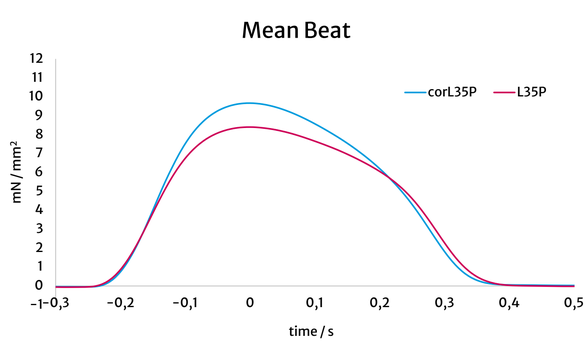


Figure 2.B

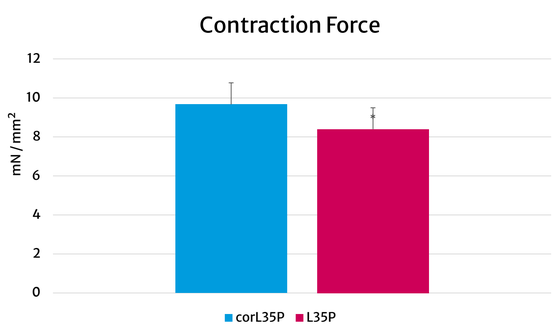


Figure 2.C

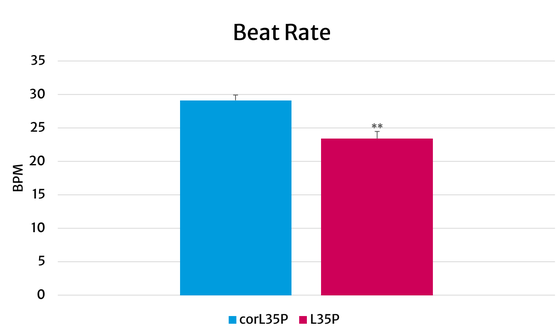


Figure 2 A-C.

Contractility analysis of L35P (magenta) and L35P corrected (blue) cell lines demonstrating different beat shapes (A) and significantly reduced contraction force (B) and beat rate (C) for the L35P diseased cell line. Data was evaluated at day 12 in culture with at least 15 replicates per cell line. Statistical analysis performed with Wilcoxon-Mann-Whitney (WMW) test.

Figure 3 A-C.
Contractility analysis of L35P (magenta) and L35P corrected (blue) cell lines showing an increase in beat duration at 50% and 90% of the L35P diseased cell line (A and B) as well as ahrrythmic events only for the L35P diseased cell line (A). Data was evaluated at day 12 in culture with at least 15 replicates per cell line. Statistical analysis performed with WMW test.

Figure 3.A

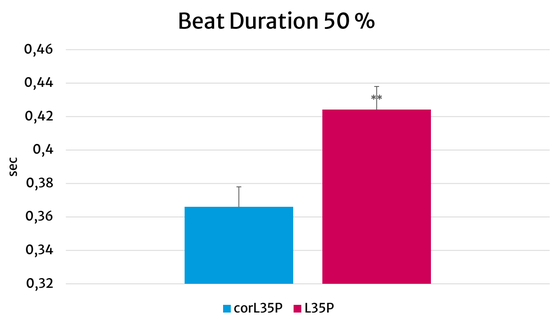


Figure 3.B

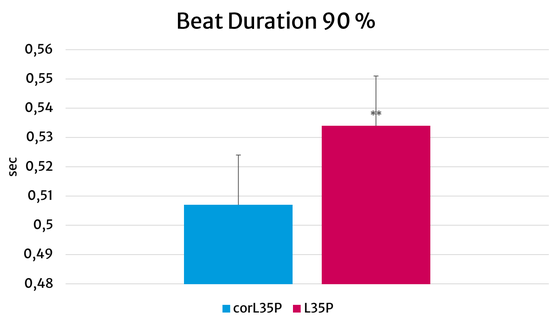
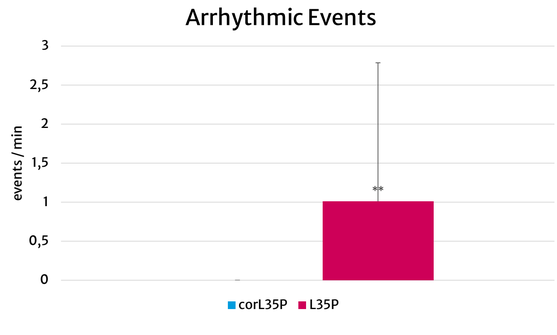


Figure 3.C



Discussion

- Functional measurements were performed to assess key contractile parameters. The L35P mutant cell line showed the following differences in comparison to the isogenic healthy control
    - Significantly reduced contraction force
    - Lower spontaneous beat rate
    - Prolonged contraction duration
    - Increased frequency of arrhythmic events

- These results demonstrate the strong negative impact of the LMNA L35P mutation on cardiac contractility and point to a substantial disruption of cardiac electromechanical integrity associated with the LMNA L35P mutation

- The study underscores the value of human iPSC models and advanced microphysiological systems for investigating laminopathy disease mechanisms and supporting therapeutic development and testing