Familial Hypertrophic Cardiomyopathy (HCM) is a primary disorder of cardiac muscle, and always accompanied with arrhythmic heartbeats. It is the most common autosomal dominant cardiovascular disease, with a prevalence of 1:500. The overall annual mortality rate of HCM is 1-5%.[1,2,3].

Mutations in over 11 genes, most of which encode sarcomeric proteins, have been identified in HCM patients. Mutations in β-mysin heavy chain (β-MHC or MYH7) account for approximately 45% of all identified HCM cases.[4] Although medications and surgery can partly improve symptoms, no specific treatments to prevent or arrest the development of HCM are available.

HCM associated arrhythmias are caused by the electrical remodeling in the heart.[5] Despite the progresses in HCM study, a remarkable deficit still exists in understanding of the molecular mechanism, which leads from sarcomeric mutations to the diverse HCM disease phenotypes.

Currently, most mechanistic studies of HCM have been conducted in model systems, including transgenic and gene targeted mice.[6] The difficulty to obtain heart tissues from healthy and HCM human hearts is the major obstacle for studying HCM using human cells.

Can Familial Hypertrophic Cardiomyopathy (HCM) be modeled with human induced pluripotent stem cells (iPSCs)?

What is the underlying mechanism of HCM?

**METHODS**

**I. HCM Patient-Specific iPSCs and Cardiac Differentiation.** Skin biopsy was collected from a 37 year old female with a diagnosis of hypertrophic cardiomyopathy. Dermal fibroblasts were reprogrammed to generate iPSCs by using retrovirus carrying Sox2, Klf4, Oct4 and Myc respectively.[7,8] Control and HCM iPSCs were differentiated into cardiomyocytes using well established Embryoid Bodies (EBs) protocol.[9,10] The EBs were dissociated at day 24 and cultured as monolayers.

**II. Cardiomyocyte Differentiation and Genome-wide Transcriptional Profiling.** Cardiac action potentials and ionic currents were recorded from iPSC-CMs. The whole transcriptomes of control and HCM iPSC-CMs were sequenced and function pathway enrichment was analyzed using Ingenuity Pathway Analysis (IPA). Electrophysiological Recordings. Cardiac action potentials and ionic currents were recorded from iPSC-derived single CMs.

**III. Calcium Handling and Ion Channels in HCM iPSC-CMs.** Calcium imaging was performed to monitor spontaneous calcium transients in HCM iPSC-CMs. Membrane currents were recorded from cardiomyocytes isolated from control and HCM iPSC-CMs using Patch Clamp techniques.

**IV. Calcium Handling and Ion Channels in HCM iPSC-CMs.** Calcium imaging was performed to monitor spontaneous calcium transients in HCM iPSC-CMs. Membrane currents were recorded from cardiomyocytes isolated from control and HCM iPSC-CMs using Patch Clamp techniques.

**V. Pharmaceutical treatment of HCM iPSC-CMs.** HCM iPSC-derived CMs were able to recapitulate phenotypes in vitro, including enlarged size, disorganized sarcomere structures and arrhythmic beating.[11,12] Importantly, patient-specific iPSCs could be used to characterize the cardiac electrophysiological abnormalities that are present in the patient in dish.[13]

**VI. Personalized study of human inherited heart disease using patient-specific iPSCs.** Heart and Lung Institute, HL093631 to GCLB. This study explored the patient-specific disease mechanism of HCM from a whole genome scope. It demonstrates the potential of using HCM iPSC-CMs for future development of therapeutic strategies. Additionally, the whole methodology established in this study could be utilized to study mechanisms of other human inherited heart diseases.

**REFERENCES**

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