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Study familial hypertrophic cardiomyopathy using patient-specific induced pluripotent stem cells

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Lab Meeting Journal Club 12th of October

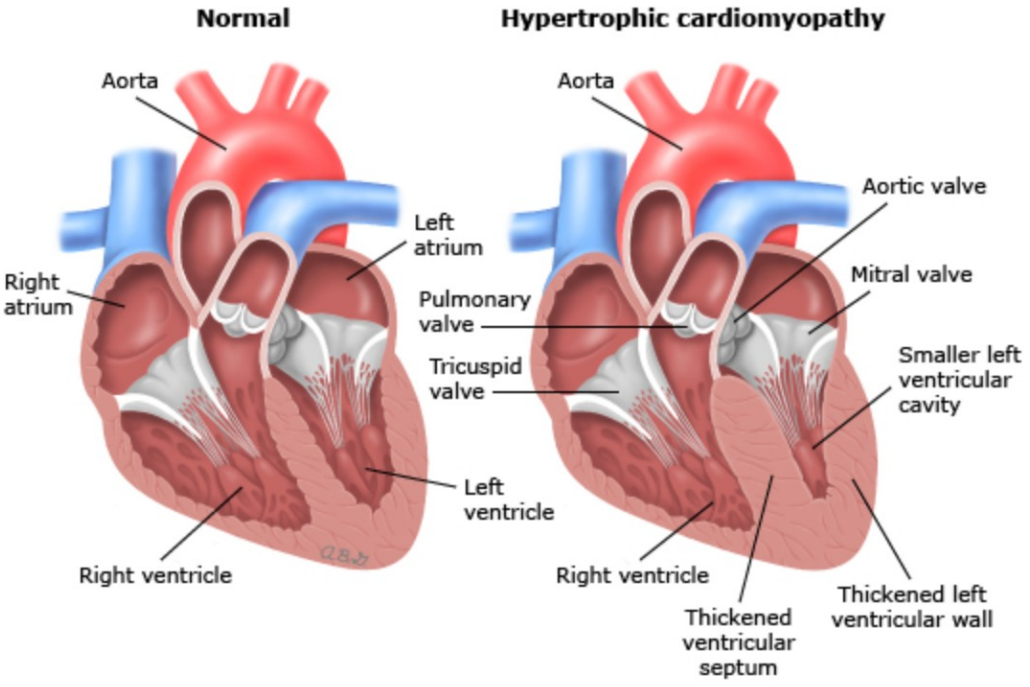
Aims

Familial hypertrophic cardiomyopathy (HCM) is one the most common heart disorders, with gene mutations in the cardiac sarcomere. Studying HCM with patient-specific induced pluripotent stem-cell (iPSC)-derived cardiomyocytes (CMs) would benefit the understanding of HCM mechanism, as well as the development of personalized therapeutic strategies.

Hypertrophic Cardiomyopathy

Common symptoms:
- Chest pain
- Dyspnea
- Dizziness and fainting
- Fatigue

Complications:
- Sudden cardiac death
- Progressive heart failure
- Systolic disfunction
- Stroke



Genetic of HCM

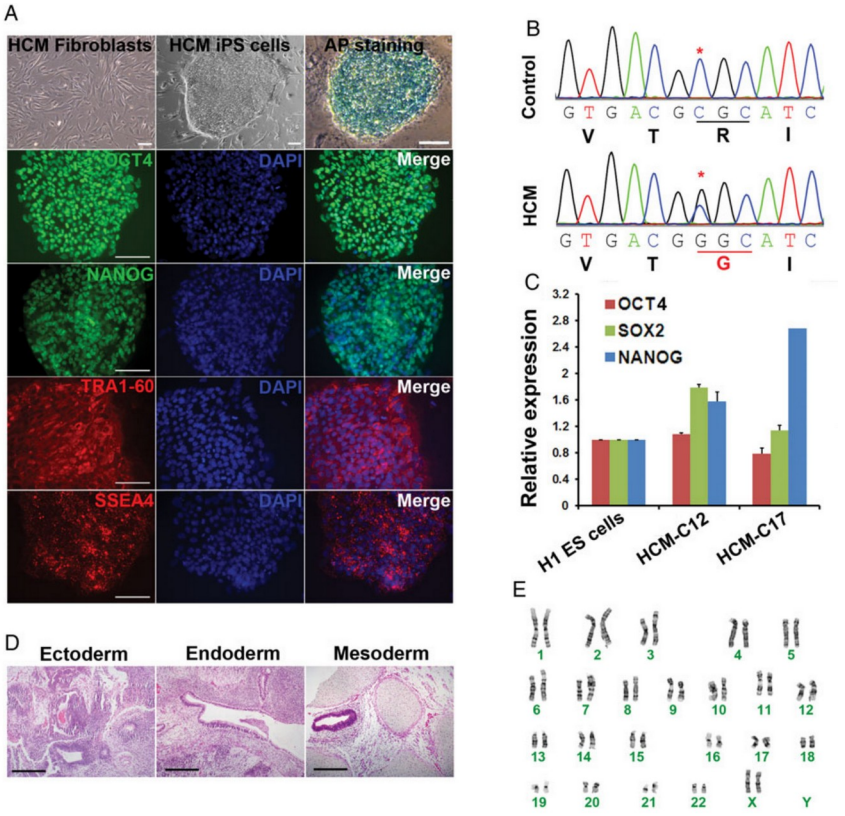
Table 2 Genes associated with sarcomere hypertrophic cardiomyopathy

Gene	Sarcomere protein	OMIM #	Frequency (%)
Thick myofilament			
MYBPC3	Myosin binding protein C	600958	~40
MYH7	β-myosin heavy chain	160760	~40
MYL2	Myosin light chain 2	160781	<1
MYL3	Myosin light chain 3	160790	<1
Thin myofilament			
ACTC1	Cardiac α-actin	102540	<1
TNNC1	Cardiac troponin C	191040	<1
TNNI3	Cardiac troponin I	191044	<5
TNNT2	Cardiac troponin T2	191045	~10
TPM1	α-tropomyosin	191010	<1
Z-disc			
ACTN2	α-2 actinin	102573	<1
CSRP3	Cysteine and glycine-rich protein 3	600824	<1
MYOZ2	Myozenin 2	605602	<1
TCAP	Telethonin	604488	<1
TTN	Titin	188840	<1

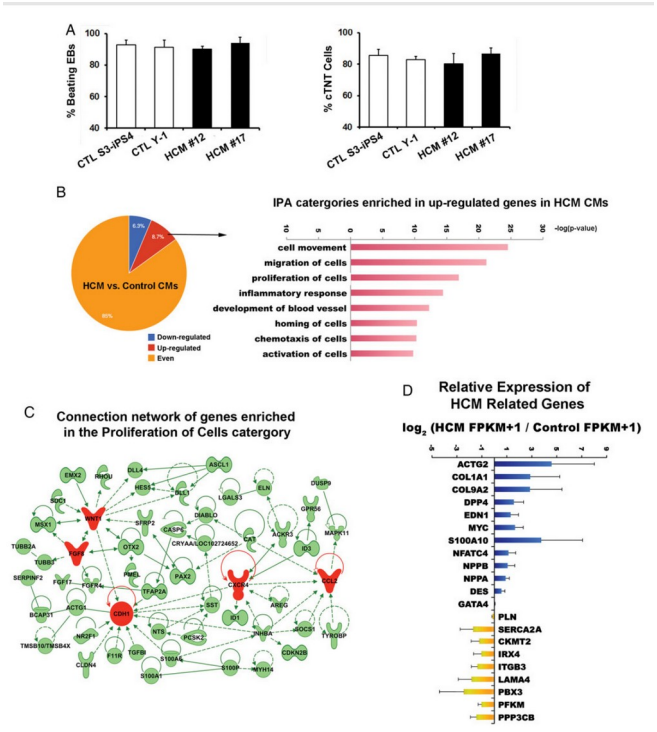
Cordula Maria Wolf. *Hypertrophic cardiomyopathy: genetics and clinical perspec tives*. Cardiovascular diagnosis and therapy, 9(Suppl 2):S388, 2019

HCM iPSC reprogramming and genotyping

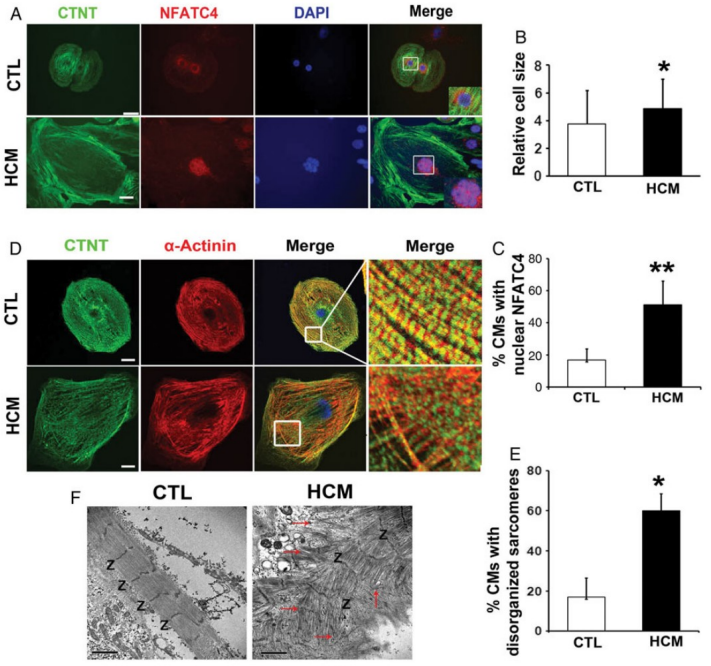
Establishment and characterization of HCM iPSCs



CM differentiation and genome-wide transcriptional profiling

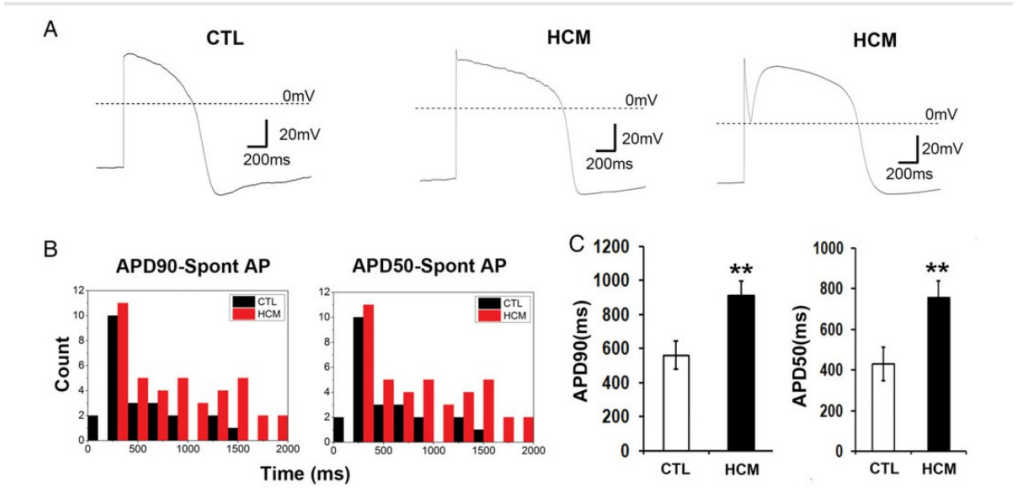


CM differentiation and gene expression profile of HCM iPSC-CMs

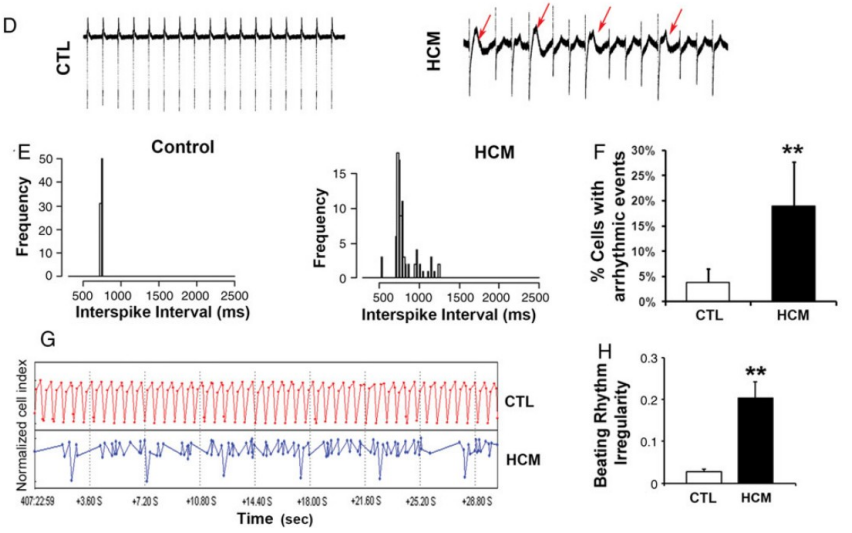


Phenotypic characterization of HCM iPSC-CMs

Electrophysiological analyses of HCM iPSC-CMs



Electrophysiological behaviour of single HCM iPSC-CMs



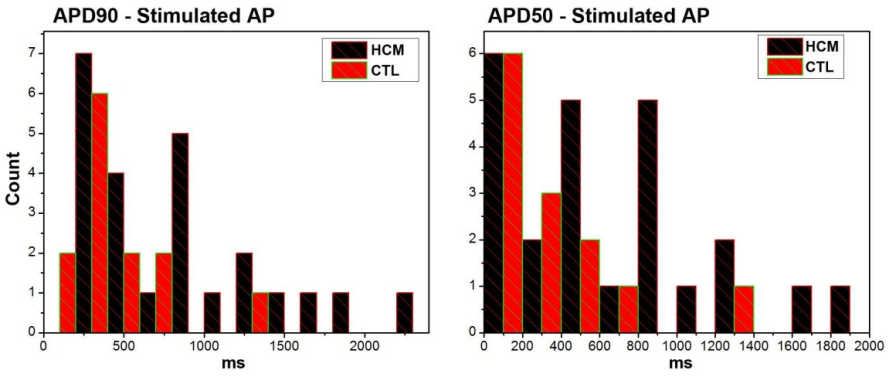
Electrophysiological behaviour of CM monolayers

Characterization of action-potentials Recording from the control and HCM IPSC-derived single cardiomyocytes.

A

		Control		HCM	
		Mean	SE	Mean	SE
Spontaneous APs	Minimum Diastolic Value (mV)	-58.441	2.212364	-59.6188	1.905717
	Mean Diastolic Potential (mV)	-49.199	2.167509	-48.2268	1.894534
	Amplitude	79.67738	6.07583	86.24236	4.119675
	Peak (mV)	24.10327	2.688481	28.25754	2.620312
	dV/dT max	7.153617	0.433891	6.84151	0.284861
	APD90 (ms)	564.824	54.6295	711.7466	43.68447
	APD50 (ms)	450.2235	99.16871	595.9008	90.7935
Stimulated APs after a train of 4 beats at 0.5 Hz	Vm (mV)	-56.0027		-58.1559	
	Amplitude	90.10721	4.353515	94.40086	2.537365
	Peak (mV)	34.10453	4.033087	36.23168	1.954102
	dV/dT max	78.99483	2.803166	86.70454	2.336756
	APD90 (ms)	560.4995	81.31584	910.3749	86.85604
	APD50 (ms)	429.3339	84.10154	756.3583	82.22055
	Capcitance	65.99569	4.762481	66.55331	4.223107

B



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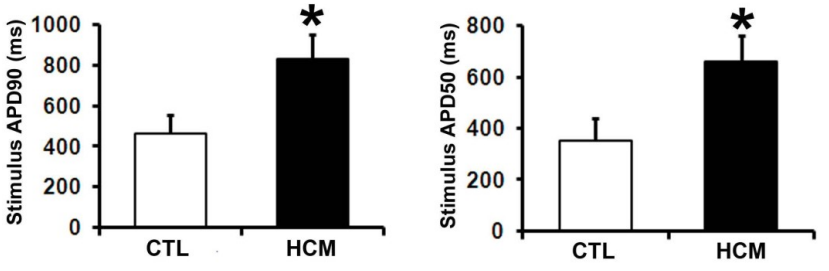
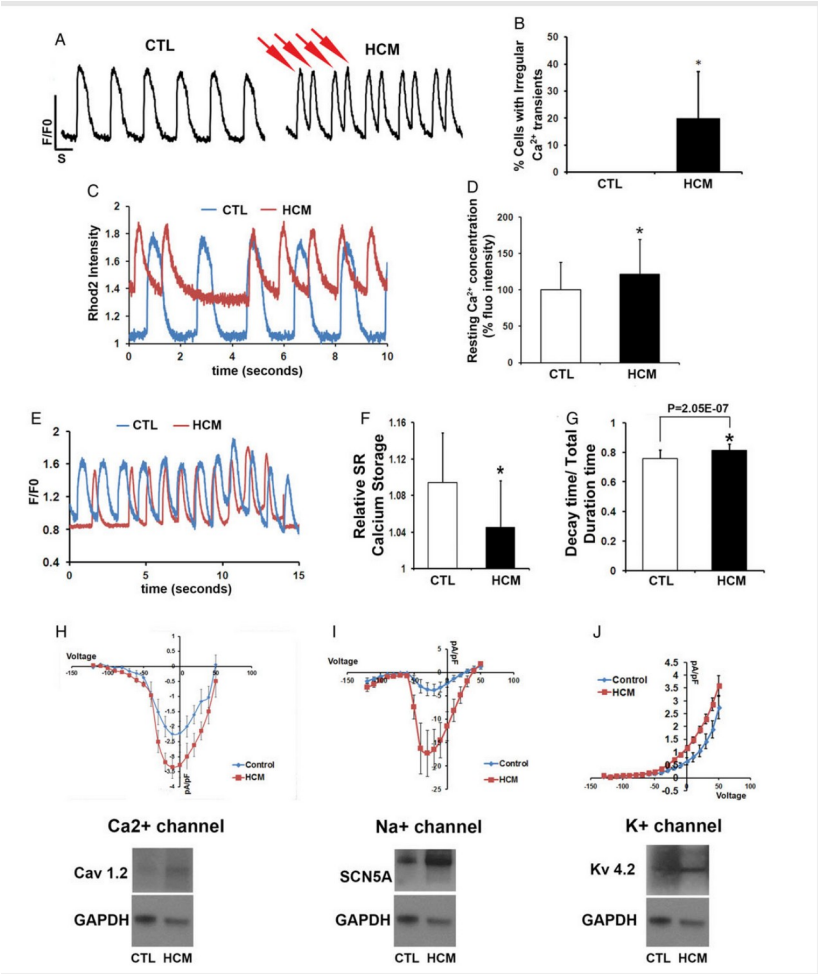
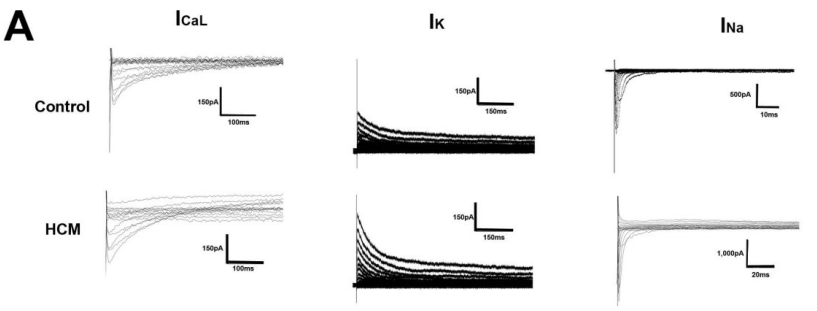


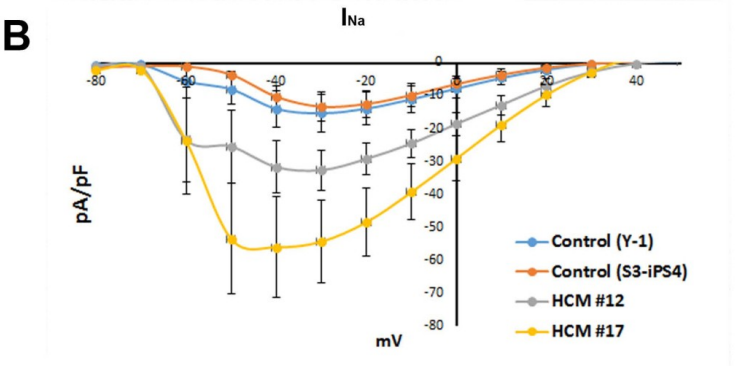
Calcium transient behaviour in HCM iPSC-CMs

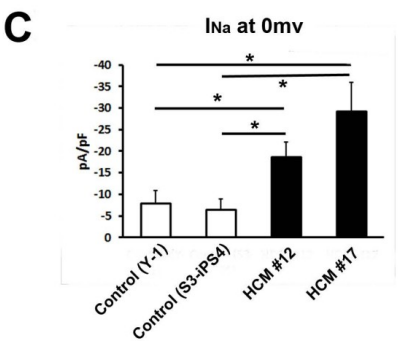
Analysis of calcium handling and ion channels



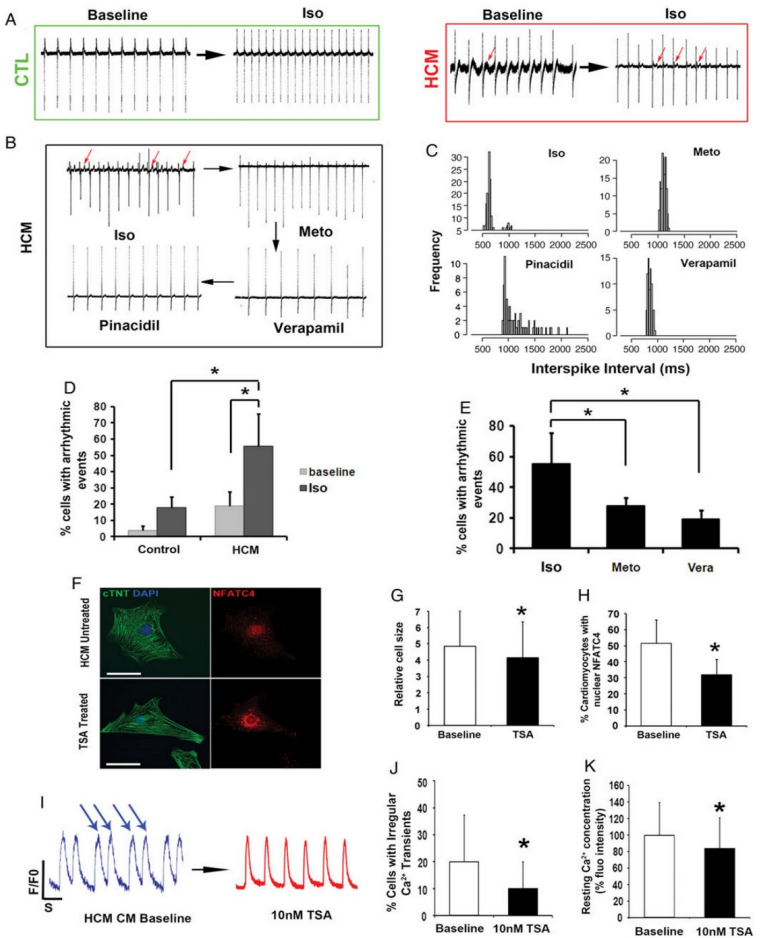
Ion channel current changes in HCM IPSC cardiomyocytes

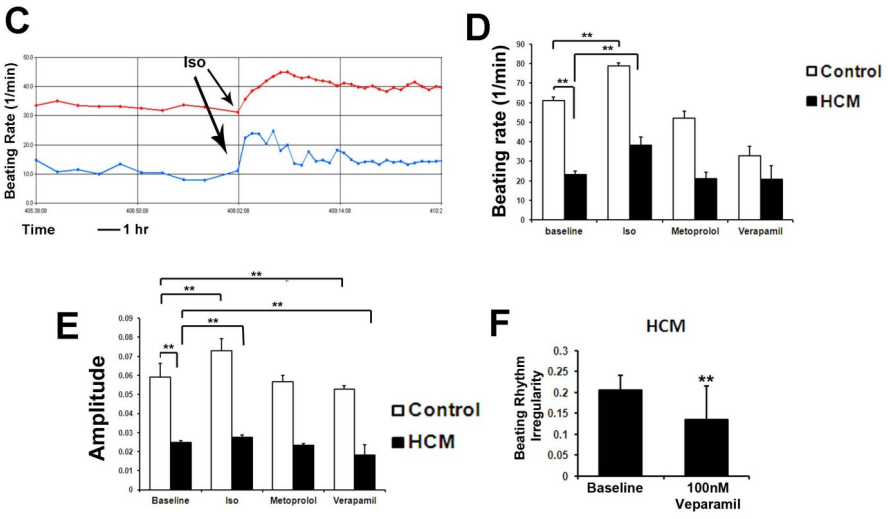






Pharmaceutical treatment of HCM iPSC-CMs





RTCA recording of iPSC-derived monolayer CMs

Research Article

Mutation-Specific Phenotypes in hiPSC-Derived Cardiomyocytes Carrying Either Myosin-Binding Protein C Or α-Tropomyosin Mutation for Hypertrophic Cardiomyopathy

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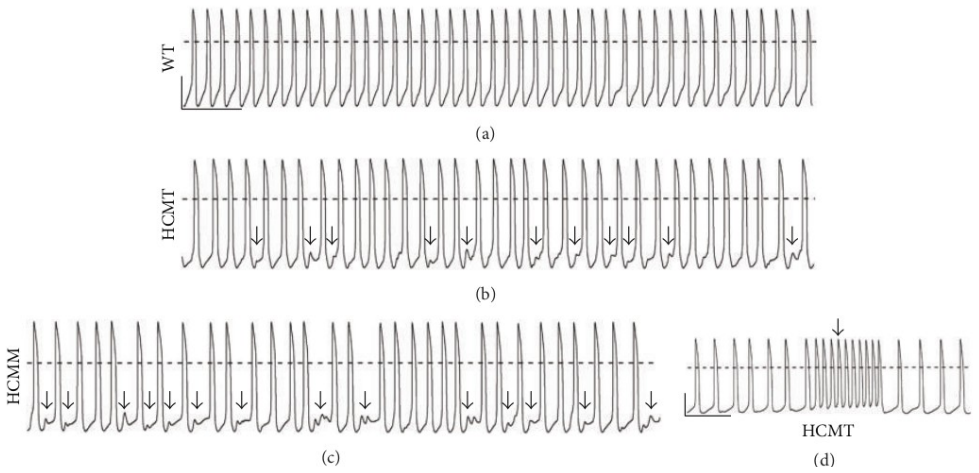
Aim: study the properties of HCM cardiomyocytes (CMs) derived from patient-specific human induced pluripotent stem cells (hiPSCs) carrying either MYBPC3-Gln1061X or TPM1-Asp175Asn mutation.

Action Potential Characteristics of WT and HCM hiPSC- Derived Cardiomyocytes



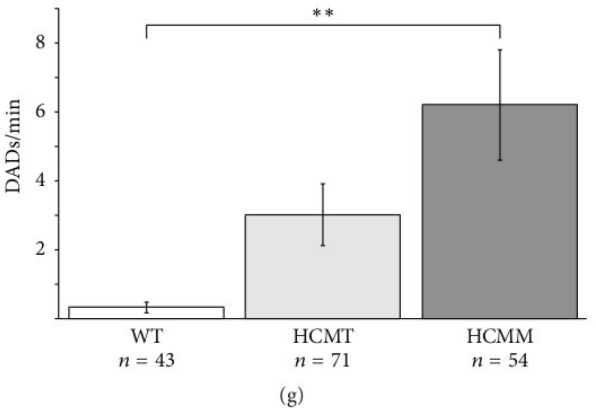


Table 3: AP properties of ventricular-like CMs derived from control hiPSC lines (WT) and from hiPSC lines carrying *TPM1-Asp175Asn* (HCMT) or *MYBPC3-Gln1061X* (HCMM) mutations. In the results, the data of each group is comprised from two separate cell lines.

Group	n	Beating rate (BPM)	APD_{50} (ms)	APD_{90} (ms)	APA (mV)	MDP (mV)
WT	43	58.1 ± 2.3	277.3 ± 13.0	323.6 ± 13.9	119.5 ± 1.1	-76.8 ± 0.8
HCMT	71	$48.4 \pm 1.5^{**}$	$372.3 \pm 13.2^{**}$	$433.1 \pm 14.0^{**}$	121.2 ± 1.1	-75.8 ± 0.7
HCMM	54	$47.1 \pm 1.8^{**}$	$319.5 \pm 13.7^{\$}$	$377.6 \pm 15.0^{*,\$}$	$124.3 \pm 1.4^{*}$	-77.9 ± 0.8

*HCMT or HCMM versus WT.
$^{\$}$HCMM versus HCMT.
$^{\$}$ or $^{*}p < 0.05$ and $^{**}p < 0.005$.