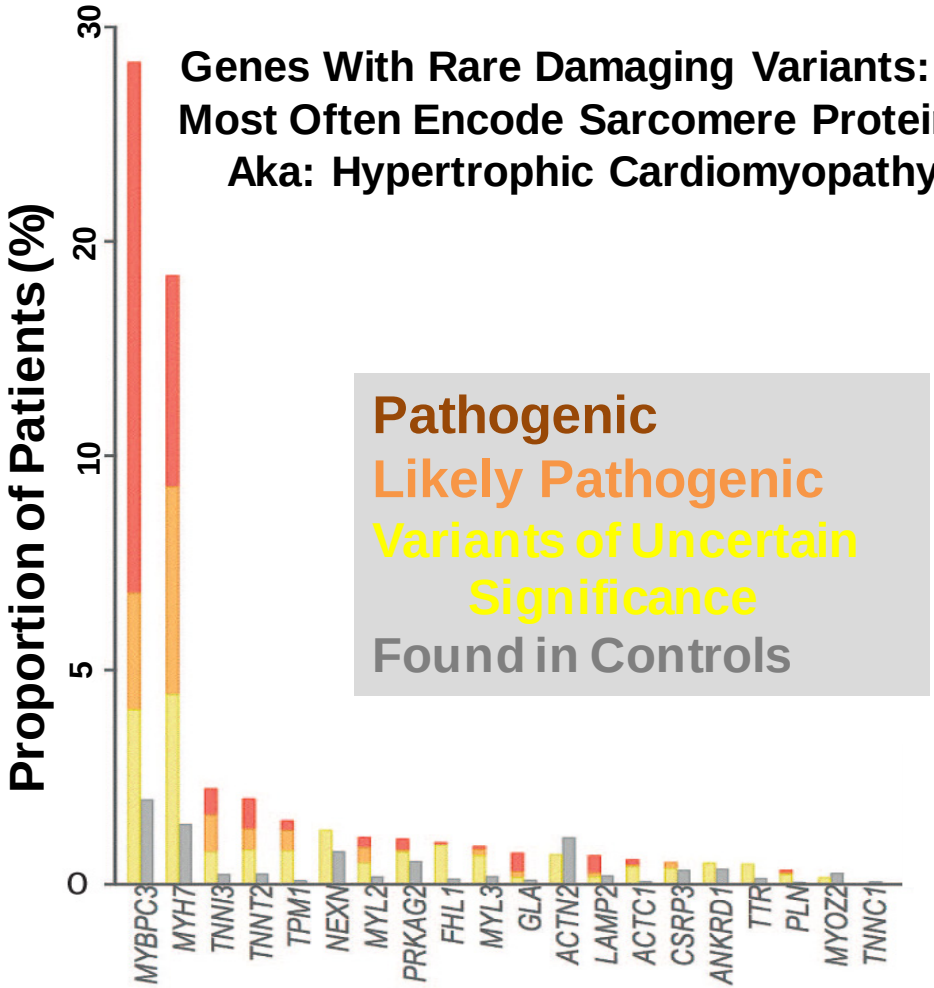
Genomics in Myocardial and Structural Heart Disease: From Generic to a Personalized Cardiovascular Approach

Christine Seidman, MD
Thomas W. Smith Professor of Medicine & Genetics
Investigator, Howard Hughes Medical Institutes

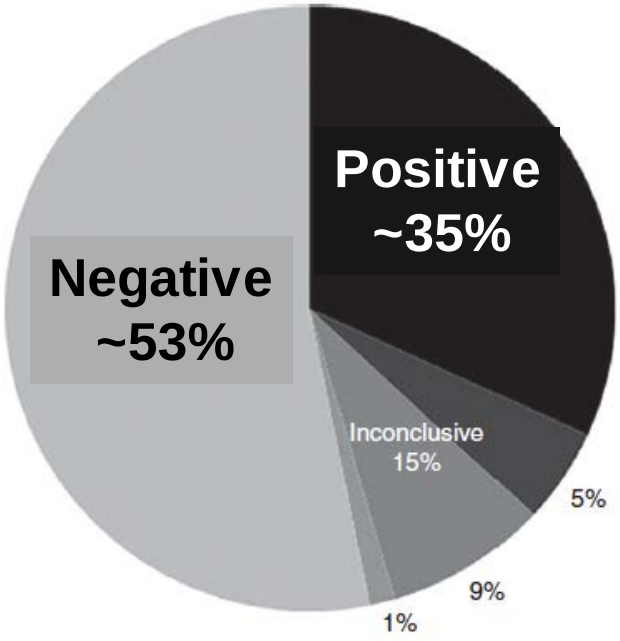
Disclosure: CES is a founder and owns shares in Myokardia Inc., a startup company that develops therapeutics targeting the sarcomere

Clinical Genetic Analyses of 7855 Cases Compared to 60,000 ExAC Controls

Genes With Rare Damaging Variants:
Most Often Encode Sarcomere Proteins
Aka: Hypertrophic Cardiomyopathy



Variants Characteristics:
Rare, Found in ≤ 1:10,000 Controls
Protein Damaging: Loss of Function
Deleterious Missense

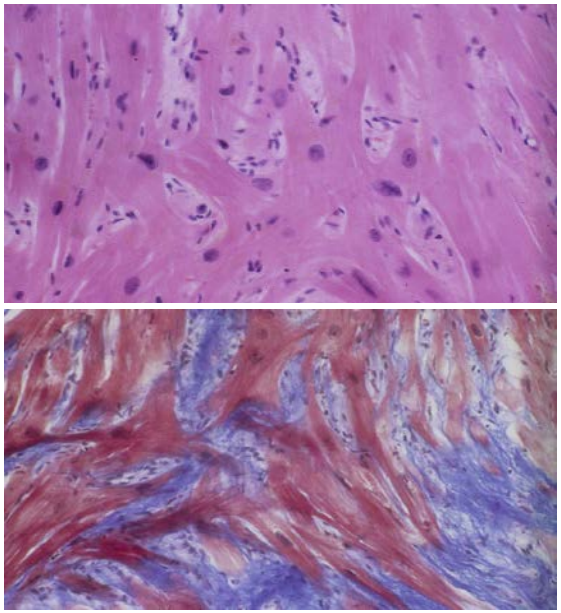


Alfares et al Genet Med, 2015
Walsh et al Genet Med, 2016

Histopathologic Impact of LVH Genes

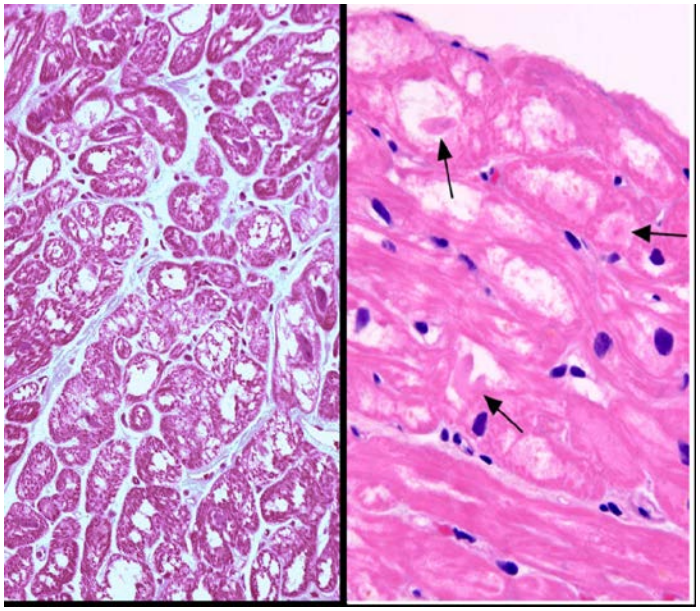
Force

MYH7, MYBPC3
TNNT2, TNNI3
MYL3, MYL2
TPMI, ACTC
ACTN, MYOZ2



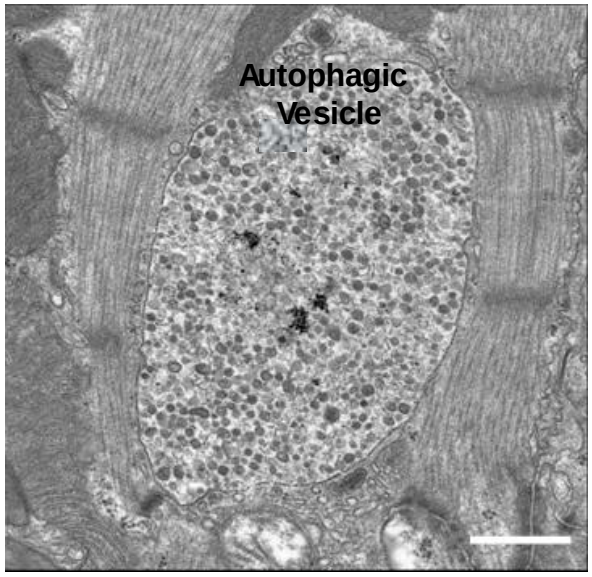
Metabolism

PRKAG2: **Glycogen**
GAA **(Pompe): Glycogen**
GLA (Fabry): **Glycosphingolipids**



Clearance

LAMP2: **Cellular Debris**
DES**: Misfolded Protein**
TTR: **Amyloid**



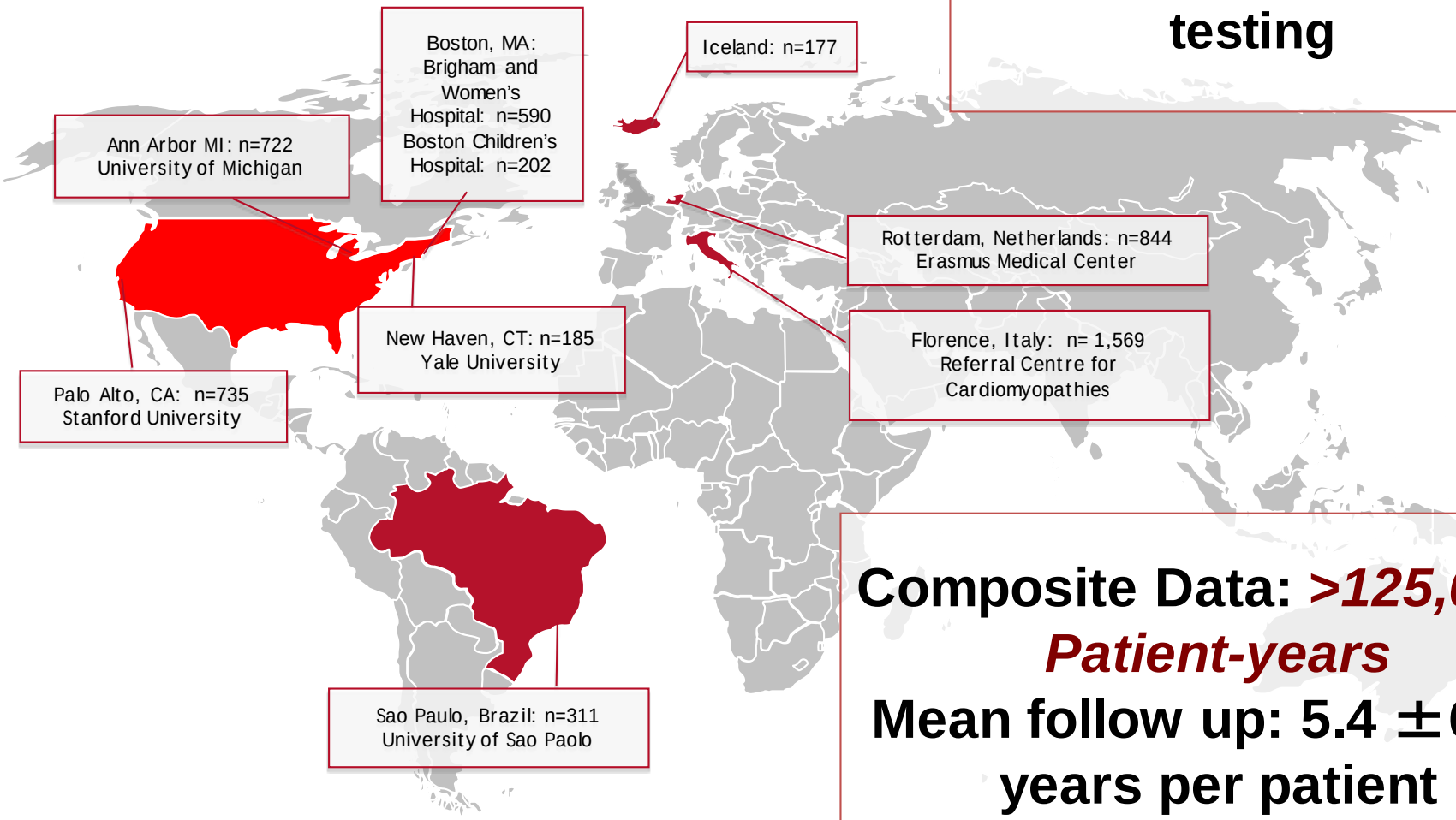
Clinical Impact of LVH Genes

Gene	Inheritance	Outcomes
Sarcomere Proteins	Dominant	Adolescent or Later Onset Atrial Fibrillation in ~25% Low SCD & HF Risk
PRKAG2 Disease	Dominant	Adolescent Onset Progressive Conduction Highest Pacemaker Rates
LAMP2	X-linked	Childood Onset, Massive LVH, Systemic Disease, VT, VF, Early Death
GLA	X-linked	Mid-Life Onset; Renal Disease, Progresses to HF (50 yrs) Therapeutic Enzyme

SHARE
FROM CARE TO CURE

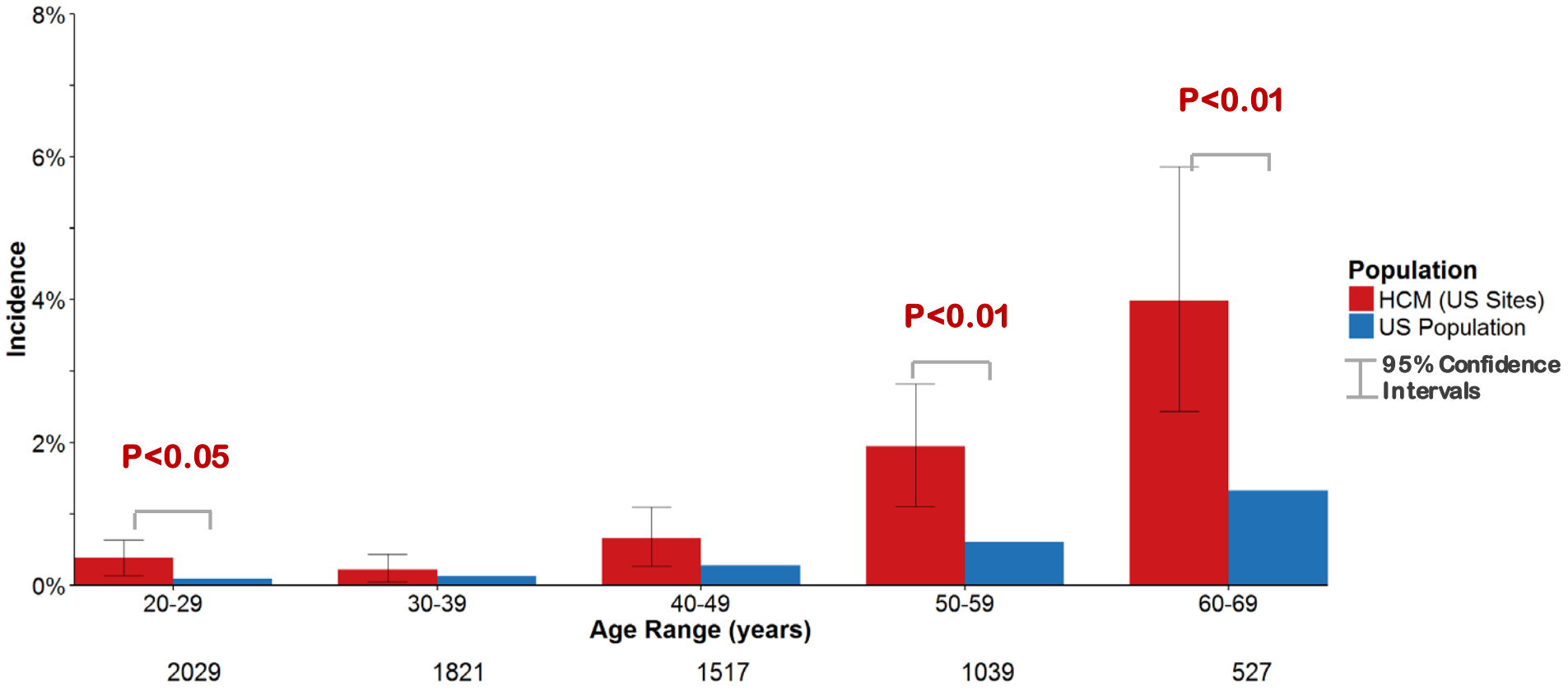
A GLOBAL INITIATIVE

More Than *6000*
HCM Patient Records
55% with genetic testing



Composite Data: *>125,000*
Patient-years
Mean follow up: 5.4 ±6.9 years per patient

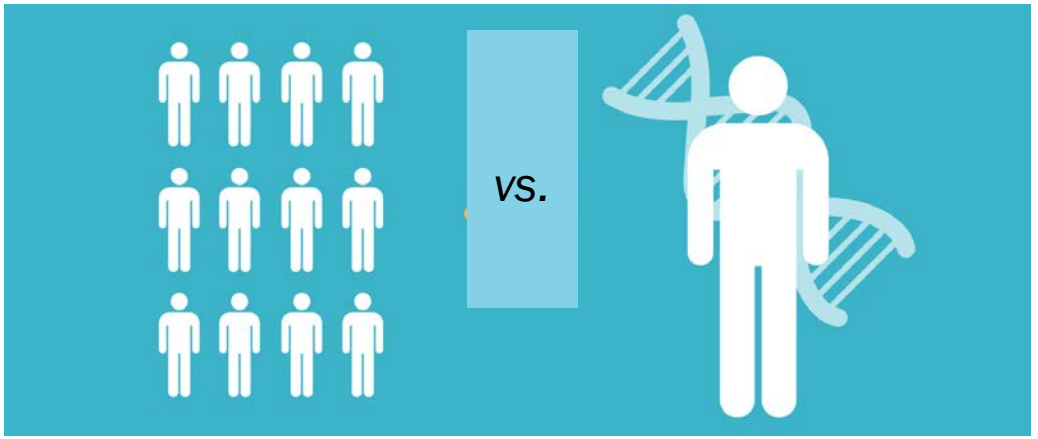
Age-Matched Mortality: 4108 HCM Patients vs US Population (1999-2014) *Ho, C. et al, in review*



Age group	Incidence in US general population (%)	Incidence in HCM patients (%) (US sites)	P-value for difference in risk
20-29	0.09	**0.39**	< 0.05
30-39	0.13	0.22	0.44
40-49	0.28	0.66	0.09
50-59	0.61	**1.95**	< 0.01
60-69	1.33	**3.99**	< 0.01

Identify individual differences and specific subgroups from broader populations

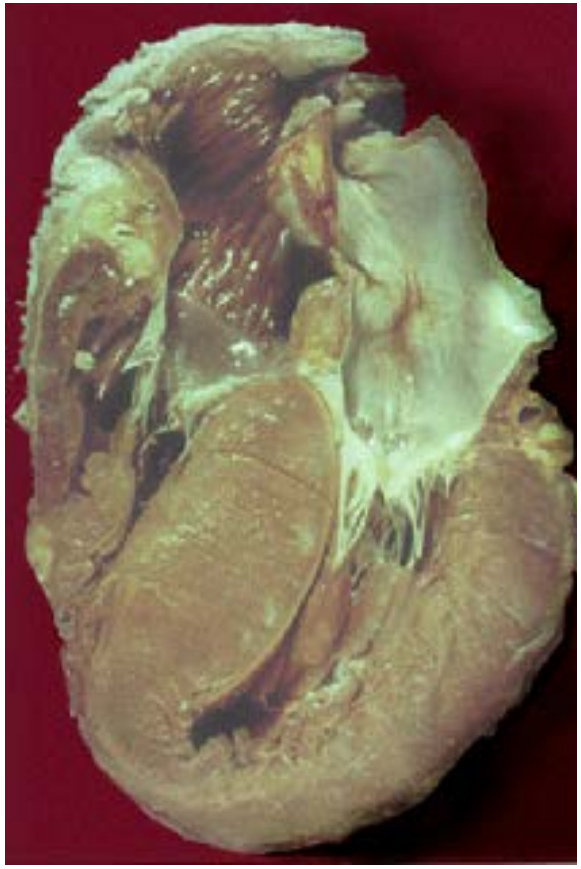
GENETICS: BRINGING MORE PRECISION TO MEDICINE

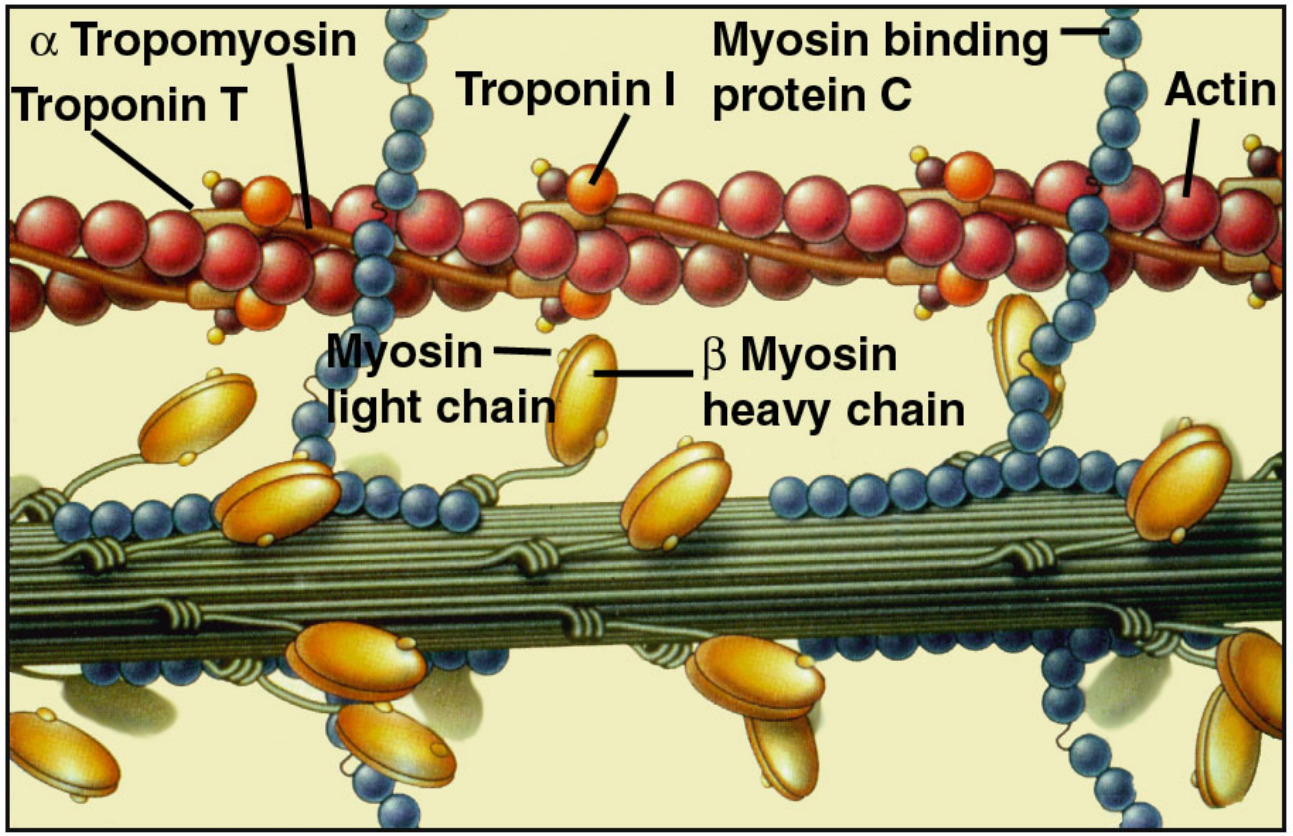


Improve traditional one-size-fits-all to individualized approach

Best for the ***average*** patient → Best for ***this*** patient

How Do Sarcomere Gene Mutations Cause Disease?



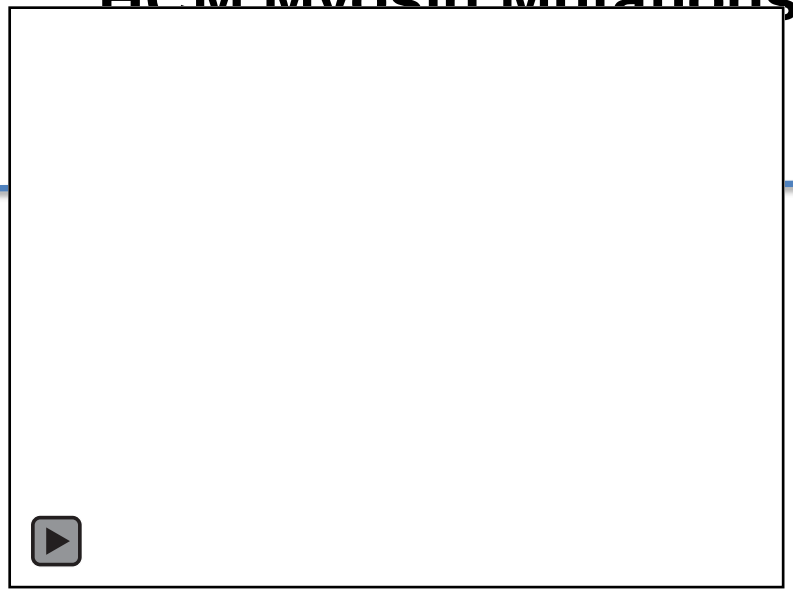


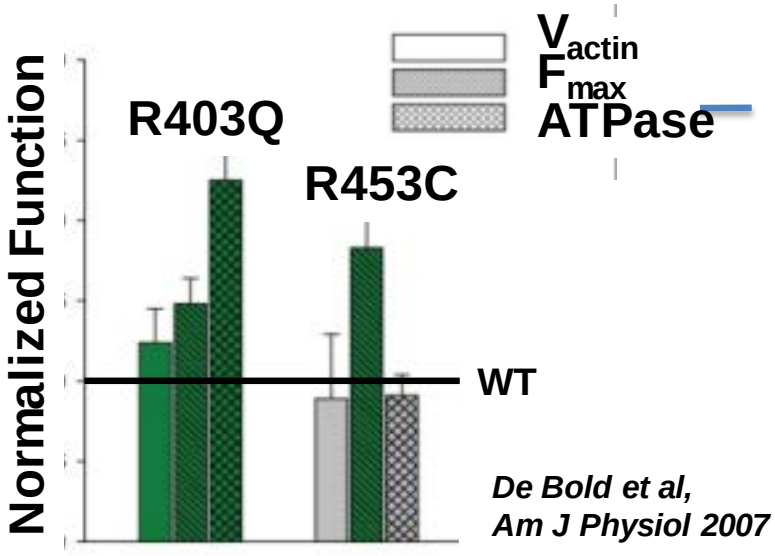
HCM Pathogenic Variants Predominate in:

Myosin Binding Protein C: Loss of Function

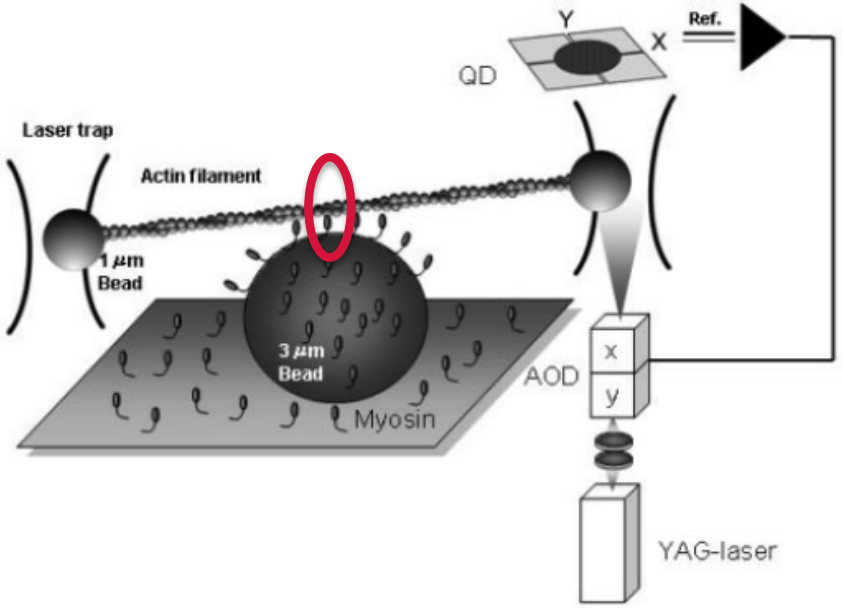
β Myosin Heavy Chain: Missense

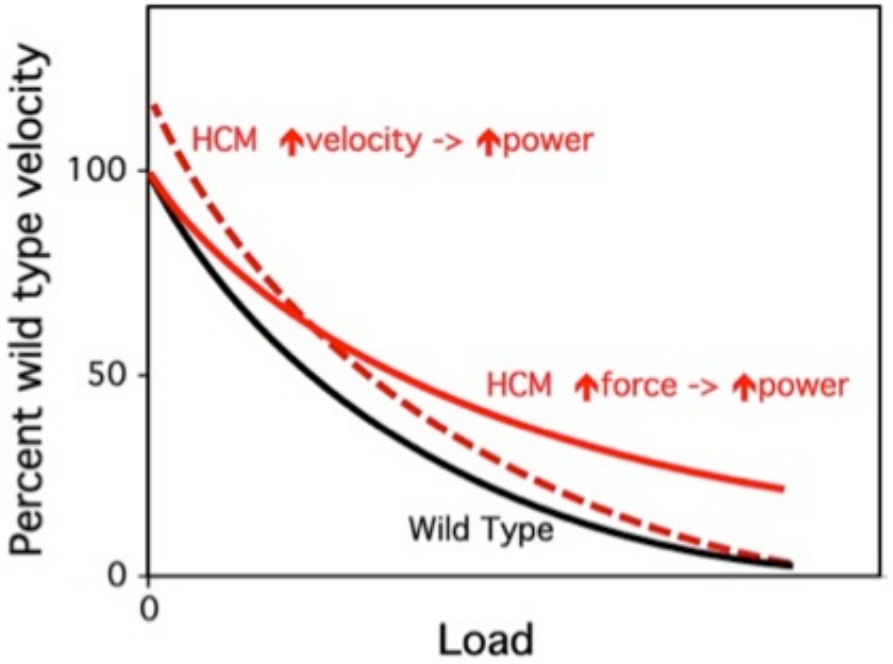
HCM Myosin Mutations Increase Sarcomere Power





De Bold et al, Am J Physiol 2007

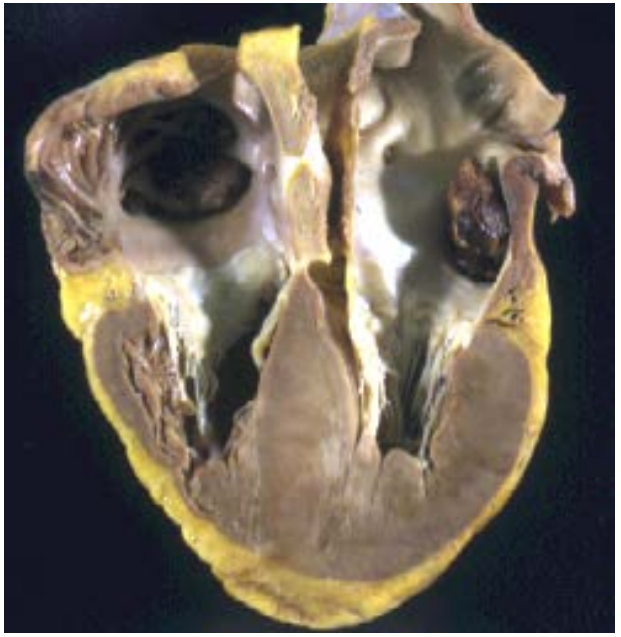


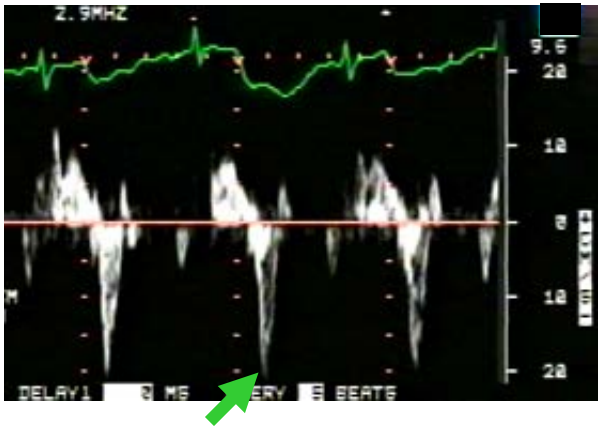


Spudich, Biophys. J 2014

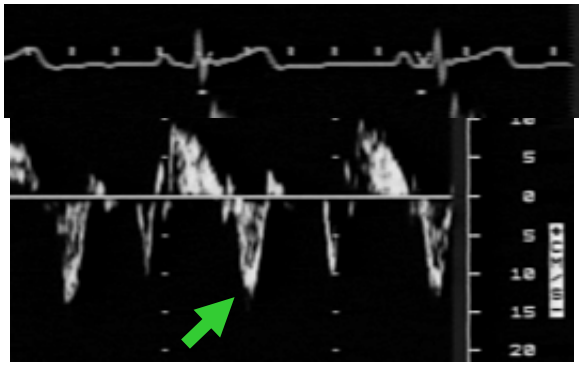
Diastolic Dysfunction Drives Symptoms in HCM

- ⬆ Pulmonary Pressure > Dyspnea
- ⬆ Atrial Pressure > Atrial Stretch
  - >> Atrial Fibrillation
  - >> Atrial Thrombus
  - >> Stroke
- ⬆ Myocardial Ischemia
  - >> Heart Failure

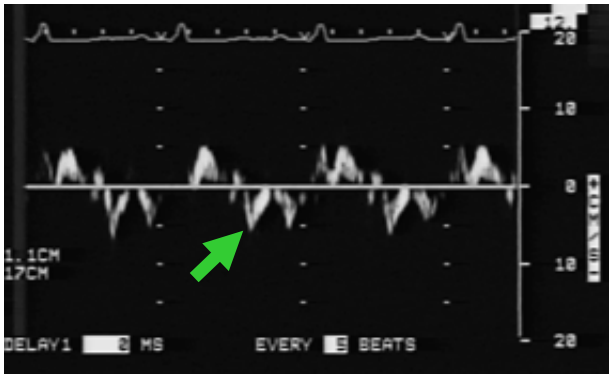




Normal
Age 23 years
E' velocity: **20.1 cm/sec**



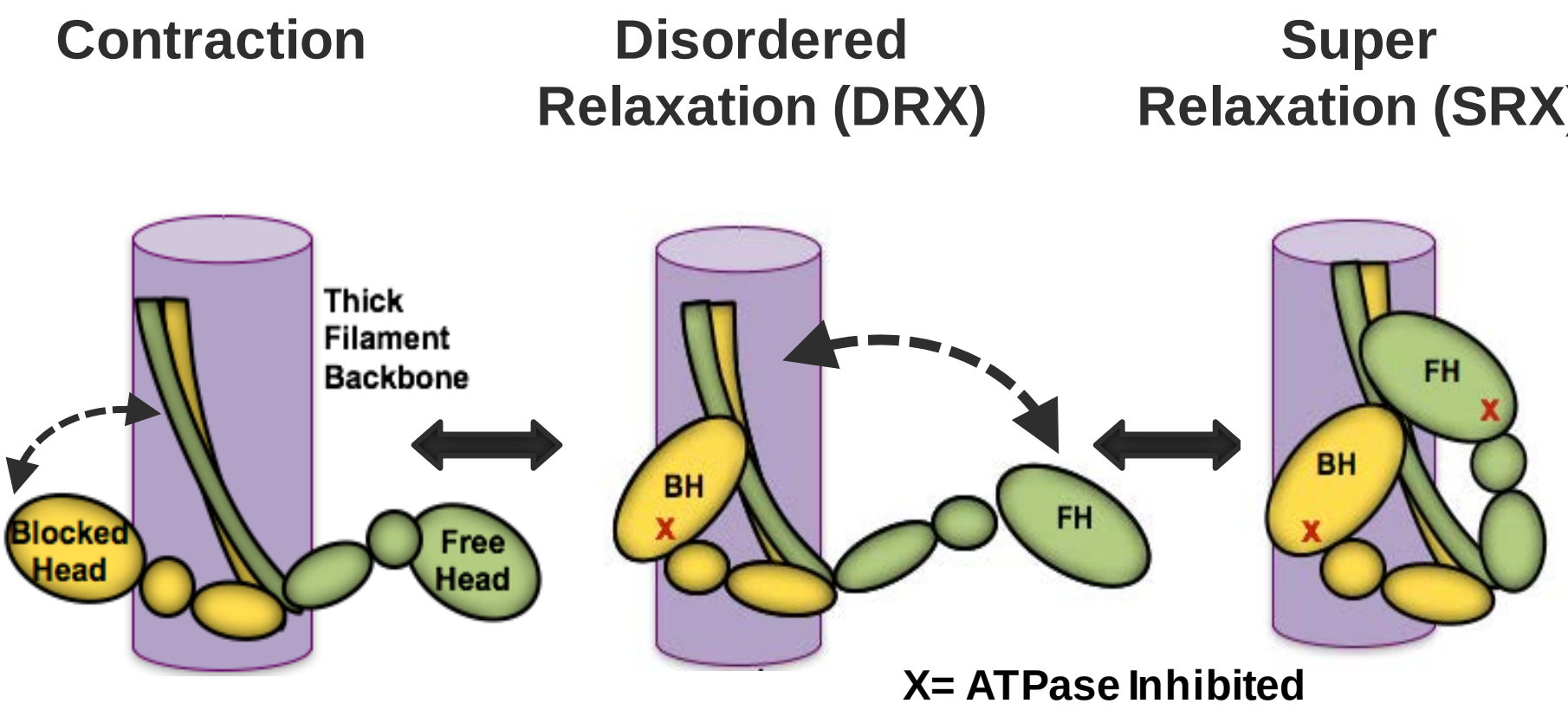
Preclinical: Mutation+ No LVH
Age 24 years
E' velocity: **10.5 cm/sec**



Overt HCM
Age 35 years
E' velocity: **5.2 cm/sec**

Ho et al., Circulation 2002

Cardiac Cycle: Contraction & Two Phases of Relaxation



Vibert & Craig, J Cell Biol; 1985,
Woodhead et al, Nature 2005
Alamo et al eLife 2017

Do HCM Variants Alter SRX and DRX Interacting Residues?

(Alamo et al eLife. 2017)

Variant Analyses in 6112 HCM and 1315 DCM Patients and 33,370 Controls

Analyses in 6112 HCM Patient Analyses:

Myosin:

Pathogenic Variants: 78% alter Interacting Residues (p=5.25e-13)

Likely Path Variants: 44% alter Interacting Residues (p=7.04e-06)

ELC and RLC:

Pathogenic Variants: <u>All</u> alter Interacting Residues

71% HCM Mutations alter Charge of Normal Residue

Analyses in Other Cohorts:

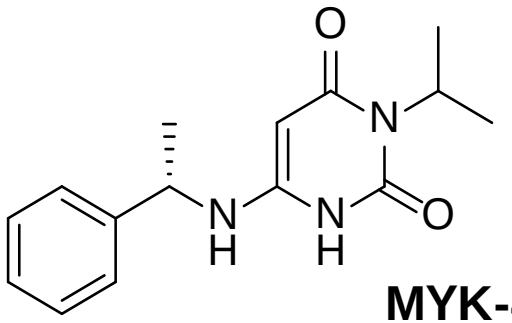
1315 DCM Patients: No enrichment in Interacting Residues (p=0.66)

33,370 Control Subjects: No enrichment in IHM Residues (p=0.23)

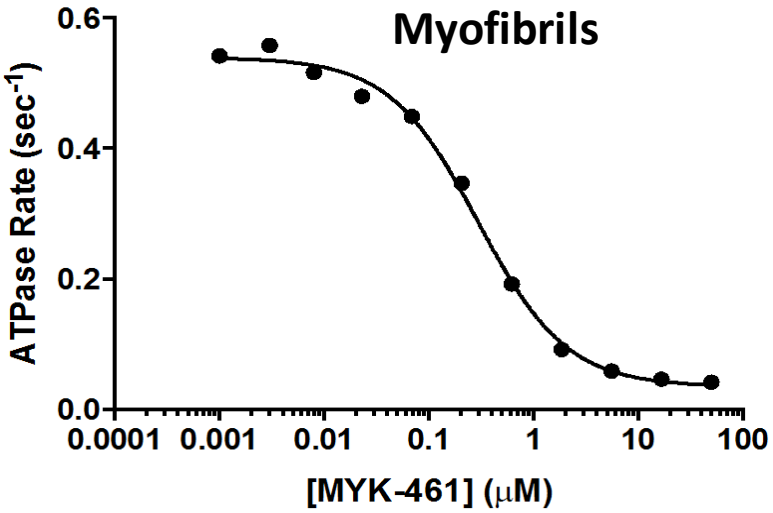
HCM Variants Increase Sarcomere Power and Impair Relaxation That Together Increase Energy Demands

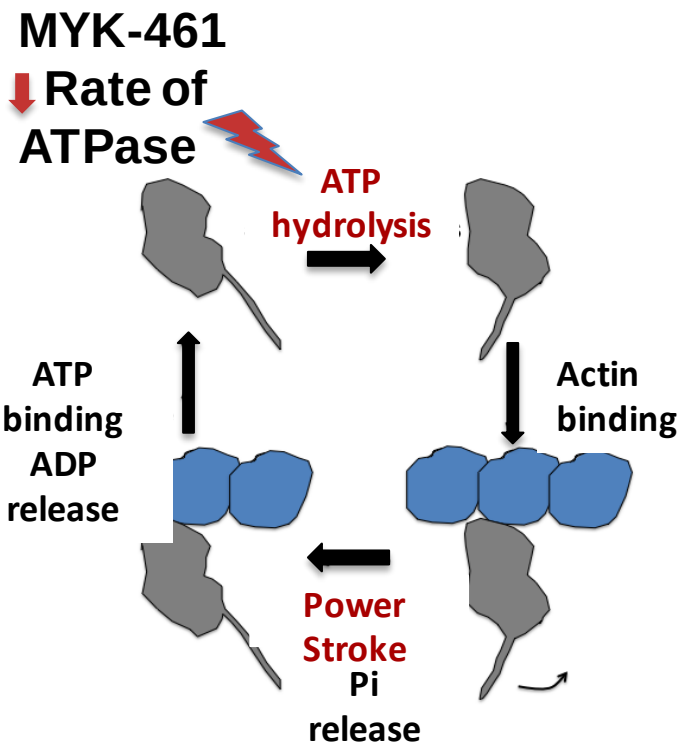
MYK-461 (Mavacamten): Inhibits Myosin ATPase Improves HCM Biophysical and Clinical Finding

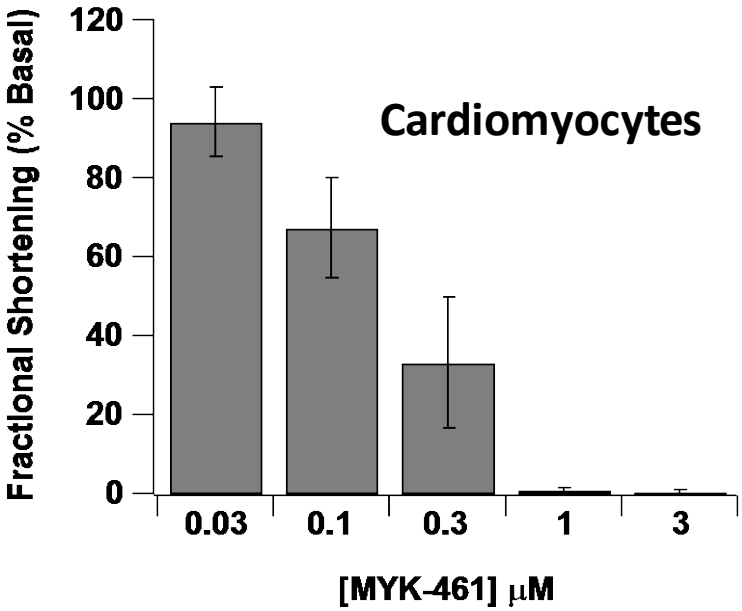
Green et al, Science 2016



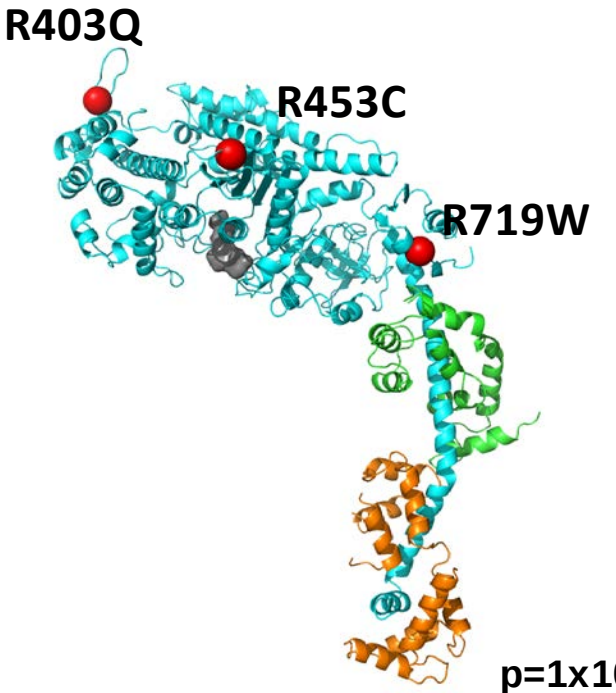
MYK-461

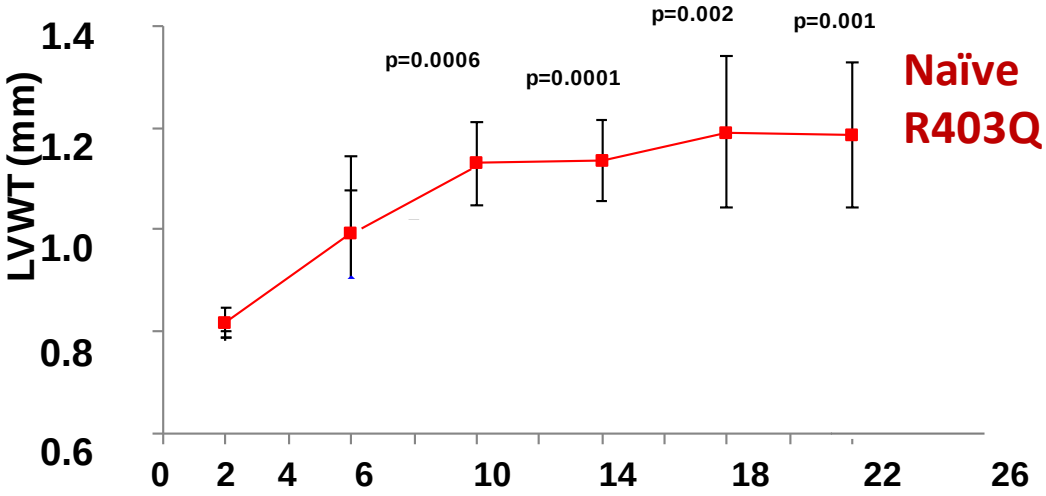


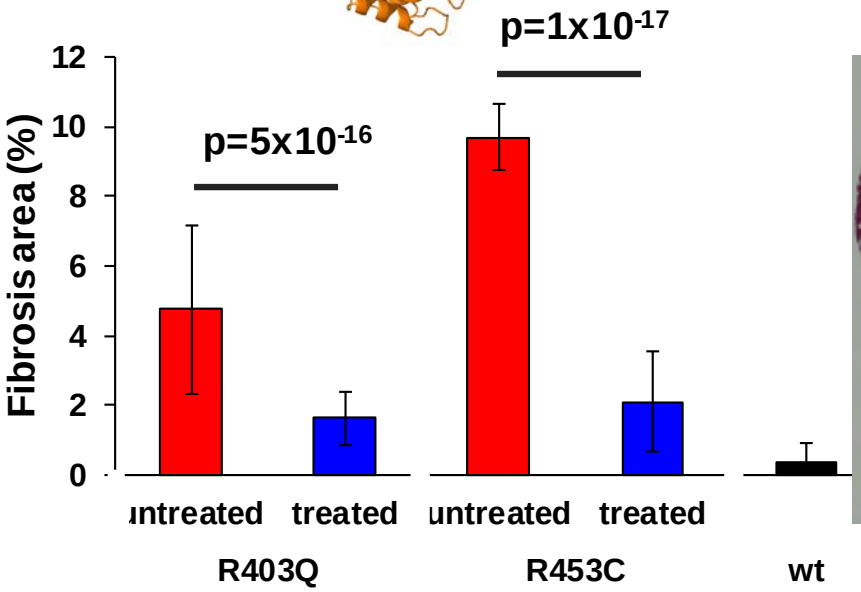


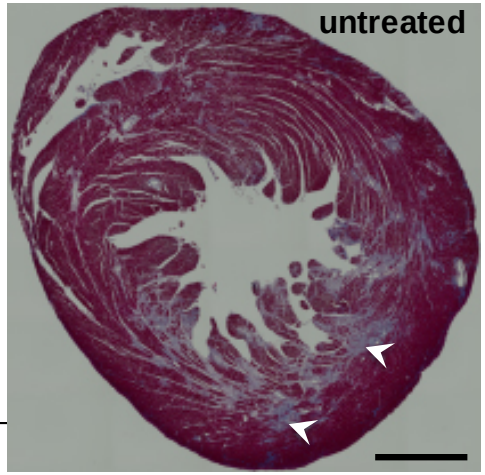


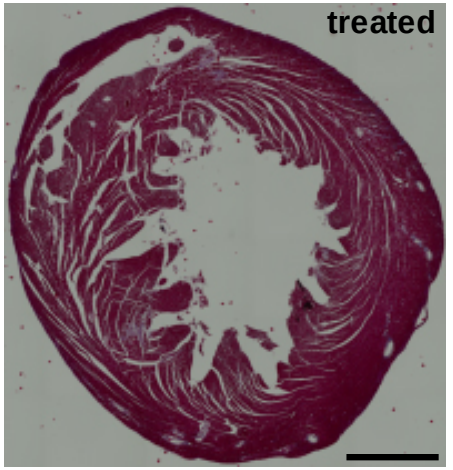
MYK-461 (Mavacamten): ↓LVH & Fibrosis in HCM Models





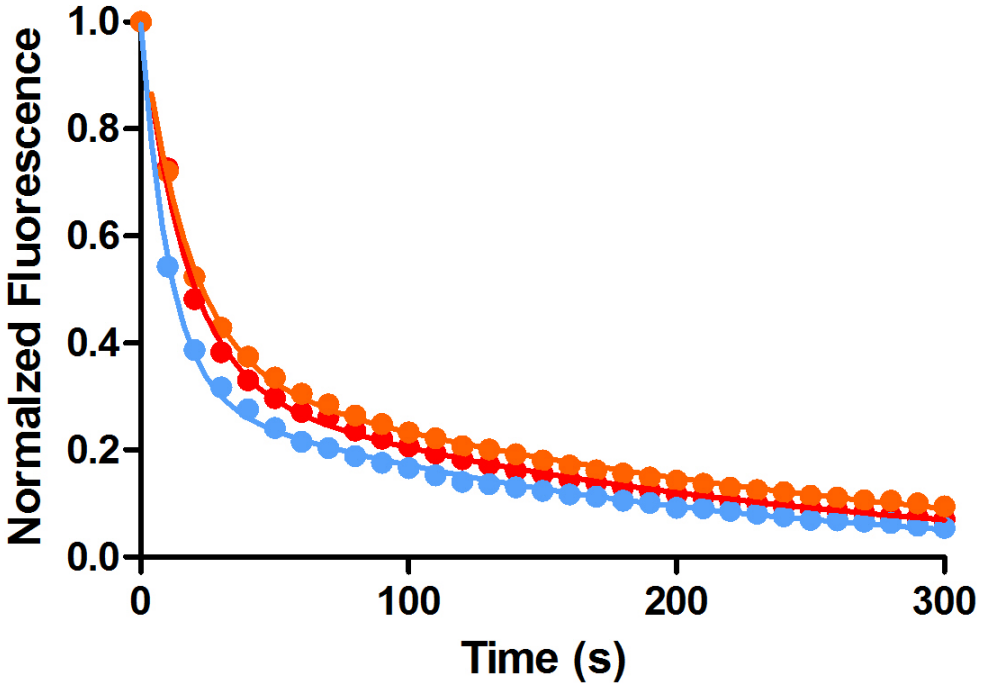


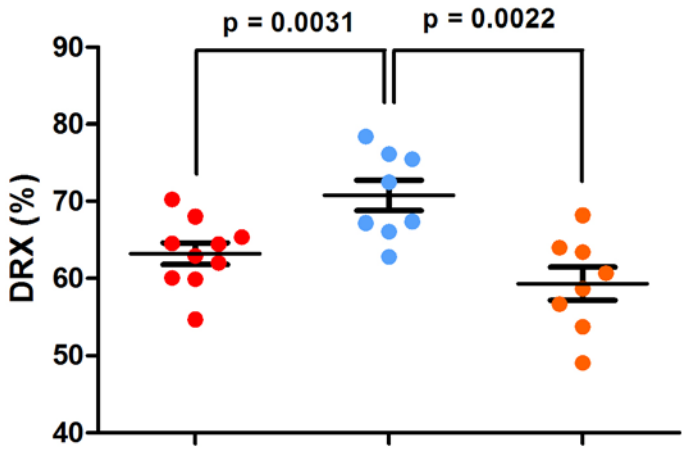


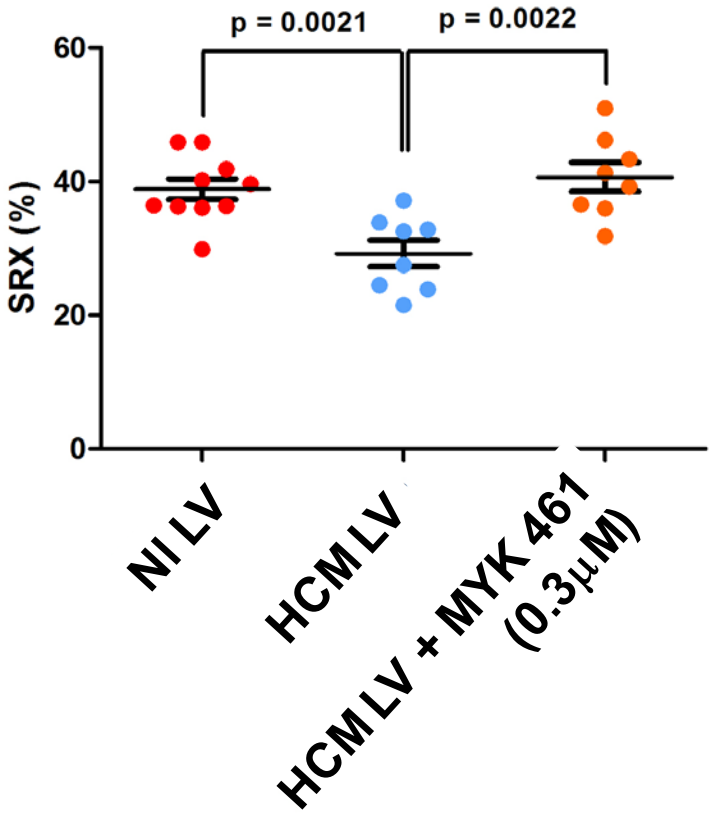


Green et al, Science 2016

MYK-461 (Mavacamten): ↑Relaxation in Human HCM LV







Translating Genetic Insights into Practice and Treatment

<u>Opportunities</u>

Improves Risk Stratification

Targets Healthcare Resources for
Patients and Family Members

Enables Mechanistic Discoveries from which
New Therapeutic Targets Emerge

<u>Challenges</u>

High Costs (but Falling Fast) & Inconsistent Insurance Coverage

Variant Interpretation Remains Incomplete (VUS)

Disease Modifiers (both Good and Bad) Remain Unknown

Unexpected, Incidental Findings

Knowledge Gaps among Physicians and Patients

Hypertrophic Cardiomyopathy

- **Mutations Inform Biophysical Processes by which the Sarcomere Functions throughout Cardiac Cycle**
  - **↑Systolic Performance: Direct Motor Function Effects**
  - **↓Diastolic Performance**
    - **↓SRX:DRX Ratio**
  - **↑ATP Consumption**

- **Sarcomere = Direct Therapeutic Target**

  Small Molecules (461) Normalize Biophysical Properties

  Potential to Treat Disorders Beyond HCM

- **Still More to Do in HCM:**

  Uncover Causes of Mutation-negative Disease

  Recruitment Ongoing:

  Seidman@Genetics.Med.Harvard.Edu

BRIGHAM AND WOMEN'S HOSPITAL
Cardiovascular Genetics Center

Clinical Team

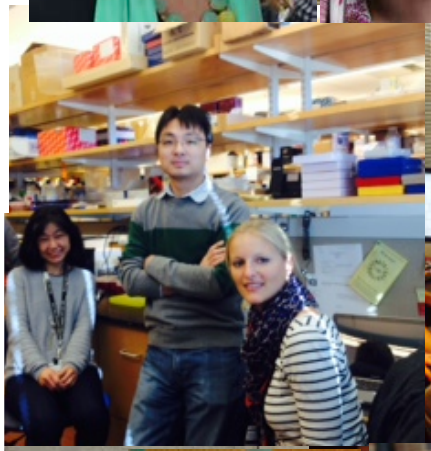
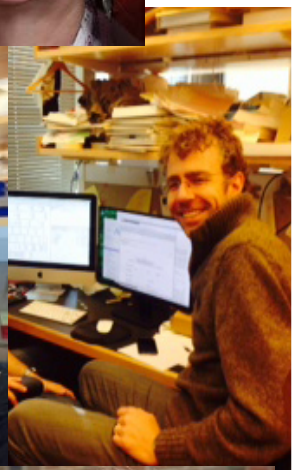
Carolyn Ho
Neal Lakdawala
Calum MacRae
Allison Cirino
Barbara McDonough





Research Team

James Ware
Christopher Toepfer
Amanda Garfinkel
Jianming Jiang
Hiroko Wakimoto

Collaborators

Raúl Padrón
Lorenzo Alamo
Robert McDowell
Marc Semigran
Leslie Leinwand
Jim Spudich