

Etiopatogeneze hypertrofické kardiomyopatie

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ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY

DONALD TEARE

From the Department of Pathology, St. George's Hospital

Received January 7, 1957

[Br Heart J.](#) 1958 Jan; 20(1): 1-8.

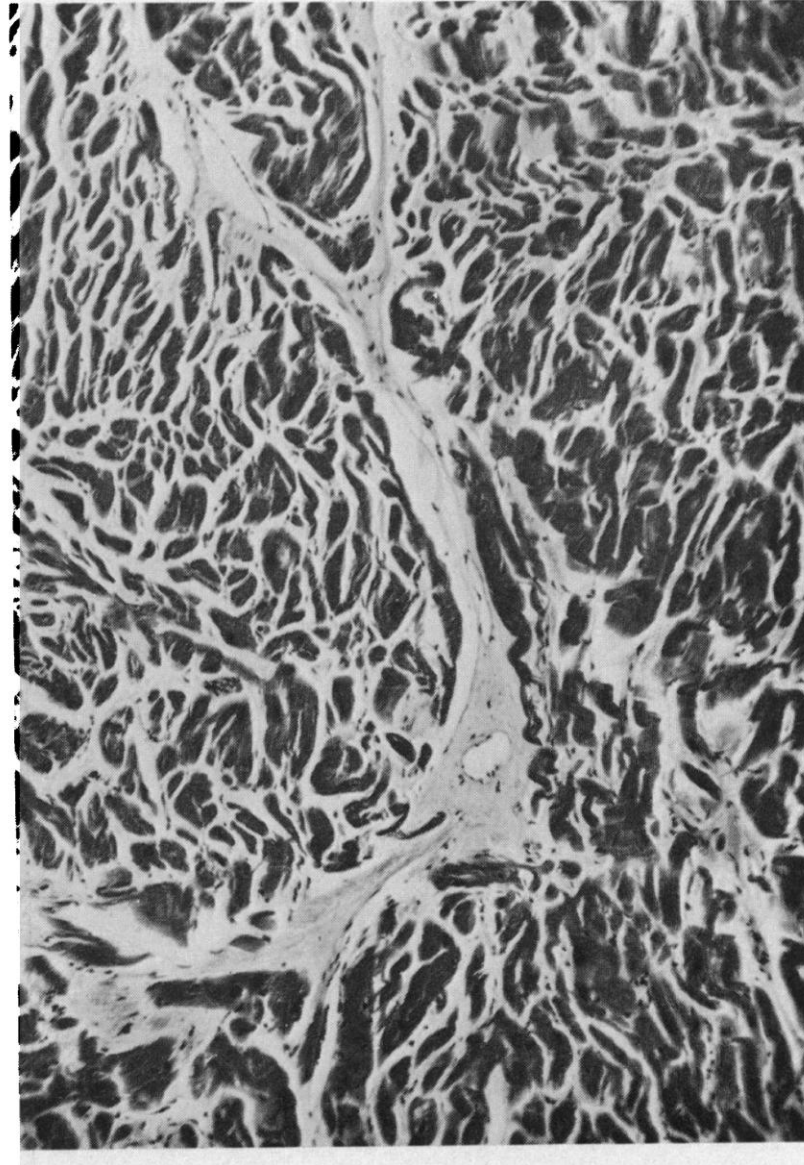
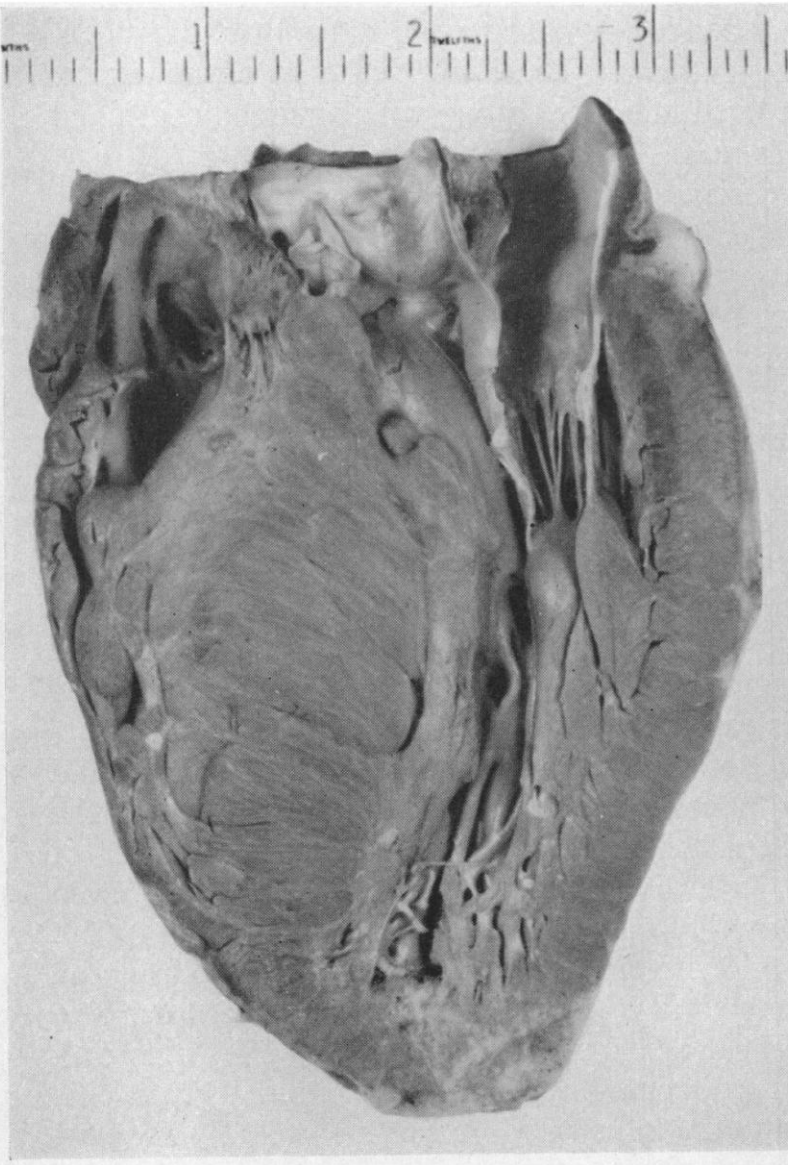


FIG. 1.—Case 1. Localized hypertrophy of the interventricular septum.

FIG. 2.—Case 1. Disordered arrangement of muscle bundles with variations in size of individual fibres (H & E $\times 80$).

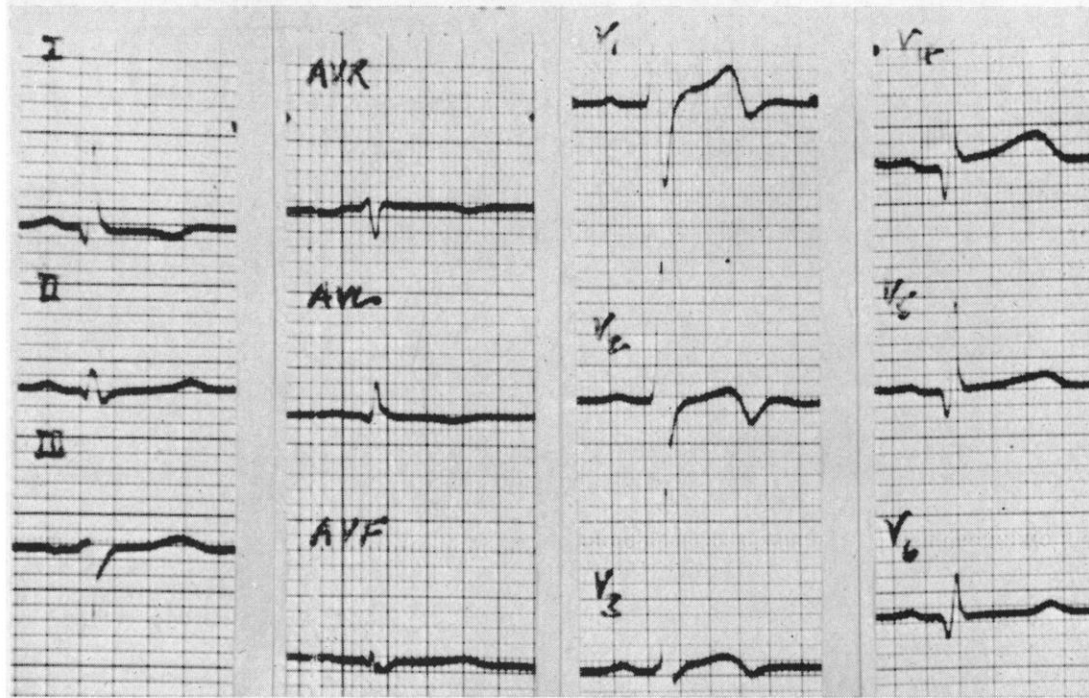


FIG. 4.—Case 3. T inversion in lead I, terminal T inversion in V1, V2, and V3, and abnormally deep Q in V4, V5, and V6. These changes indicate areas of fibrosis or abnormally functioning myocardium in the anterior and lateral walls of the left ventricle.

[Br Heart J.](#) 1958
Jan; 20(1): 1–8.

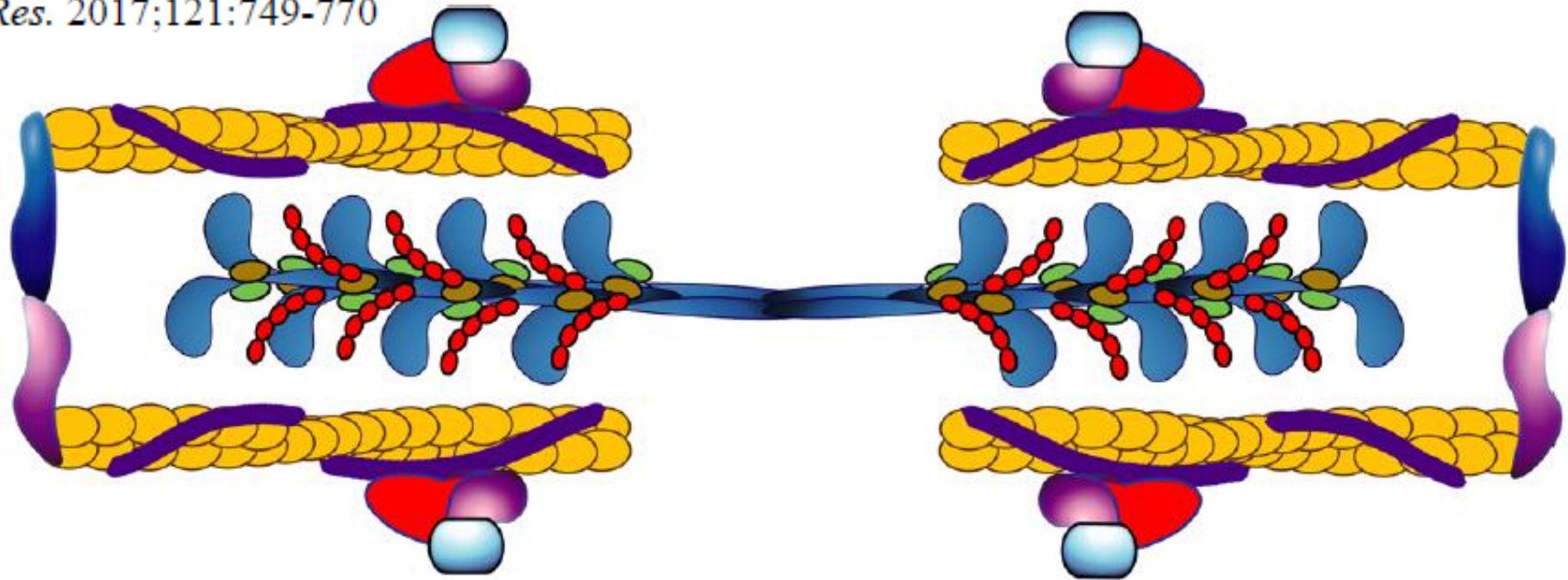
ADDENDUM

On December 13, 1956, K. C., aged 16, a brother of Case No. 5, collapsed and died while riding his bicycle. No previous medical history was available. Post mortem he was found to be a well nourished and well developed young boy whose heart was virtually identical in appearance with that of his sister, showing a localized hypertrophy affecting the anterior wall and interventricular septum. By coincidence on the day of his death his younger sister attended the outpatient department of Hammersmith hospital and was found to have signs identical with her sister. This family will be the subject of another paper.

Dr. J. F. Goodwin, Mr. Donald Ross, Dr. J. Richardson, Dr. E. W. Paul, and Dr. E. D. Acheson have all allowed me the use of clinical notes and electrocardiograms. Dr. Aubrey Leatham has interpreted the latter for me. Miss J. Underhill and Miss S. Fry have photographed the specimens and Professor Crawford has provided the photomicrographs. To all these I am most grateful for help, advice, and encouragement.

Genetické příčiny HCM

Circ Res. 2017;121:749-770



Thin myofilament
proteins
(~5%)

- ACTC1
- TPM1
- TNNI3
- TNNC1
- TNNT2

Thick myofilament
proteins
(~45%)

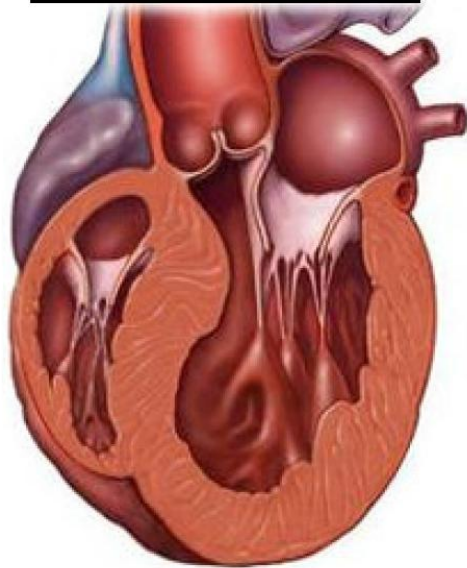
- MYBPC3 (25%)
- MYH7 (20%)
- MYL2 (<1%)
- MYL3 (<1%)

Z disk
proteins
(~1%)

- CRSP3
- MYZO2

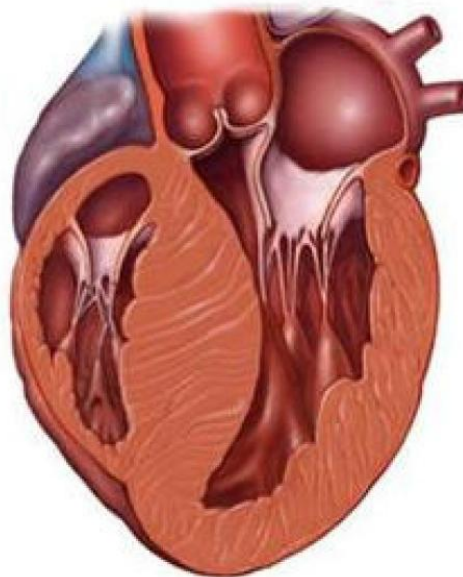
Sarkomerické mutace: korelace genotypu a fenotypu HKMP

**Sigmoidal
HCM
40 - 50%**



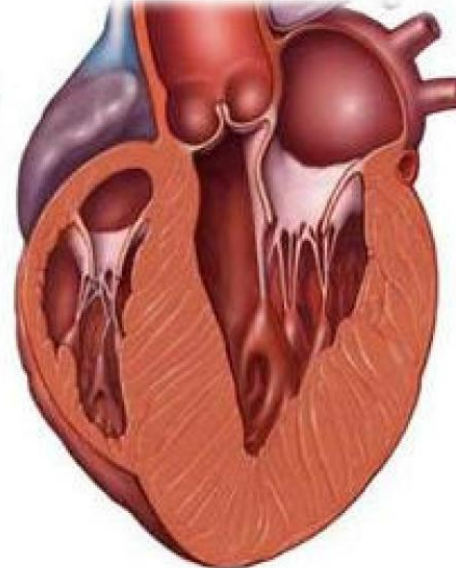
~ 10% Myofilament
Gene +

**Reverse curve
HCM
30 - 40%**



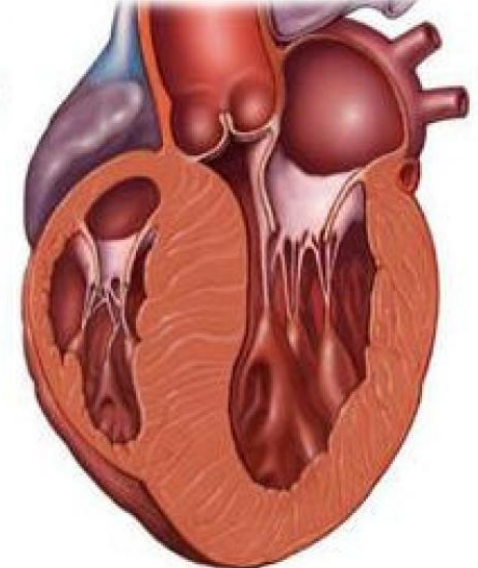
~ 80% Myofilament
Gene +

**Apical
HCM
~ 10%**



~ 30% Myofilament
Gene +

**Neutral
HCM
~ 10%**



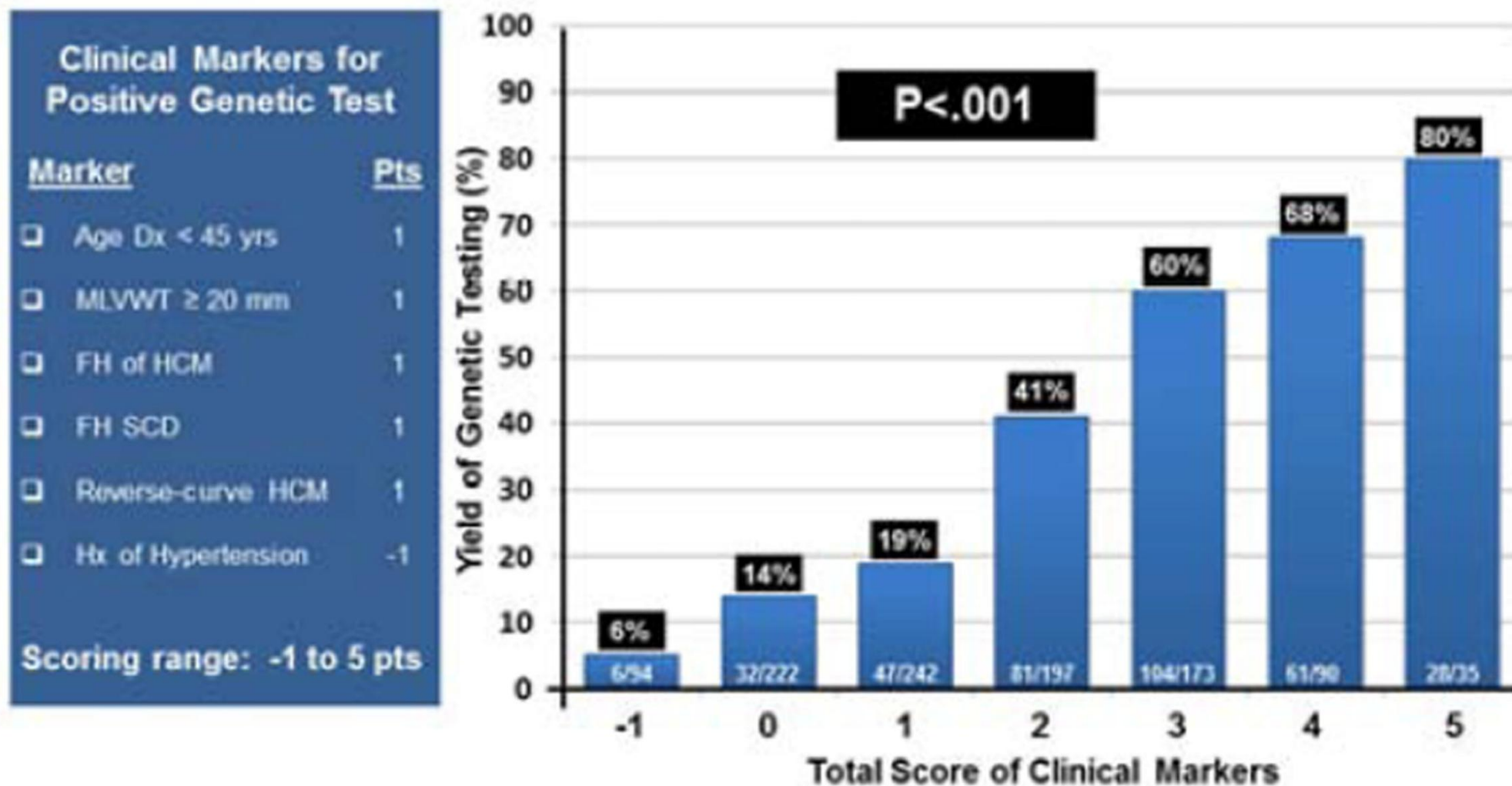
~ 40% Myofilament
Gene +

Sarkomerické mutace lze prokázat v 60% familiárních a 40% sporadických případů.

Predikce pozitivity genetického testování u pacientů s HCM podle Mayo skóre (34% genotyp pozitivní z 1053 nepříbuzných pacientů s HCM)

Bos et al.

Page 16



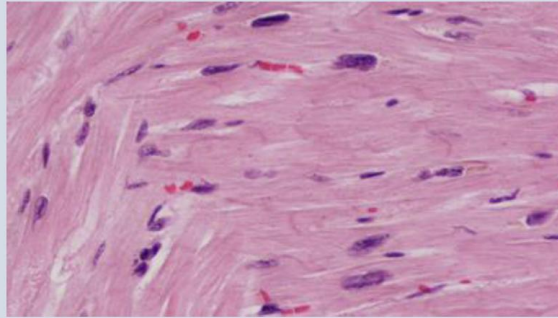
Mayo Clin Proc. 2014 June ; 89(6): 727–737.

Figure 3. Mayo HCM Genotype Predictor Score

Hypertrofická kardiomyopatie (HCM)

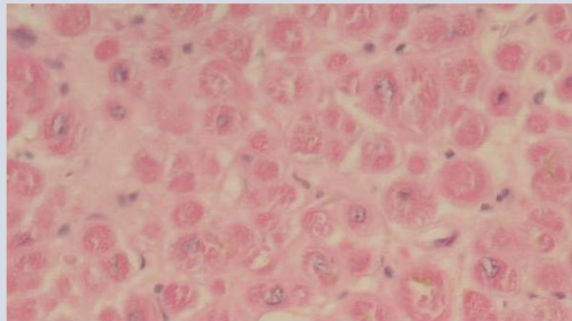
- U dospělých je definována: ztluštění stěny LKS ≥ 15 mm v jednom nebo více segmentech, které nelze vysvětlit objemovým nebo tlakovým přetížením. Event. 13-14 mm u příbuzného, pokud je rodině potvrzena HKMP.
- Časté onemocnění (1:500), které ve většině případů výrazněji nezkracuje délku života.
- Komplikace: srdečním selháním (s/bez obstrukce LVOT), NSS, fibrilace síní, tromboembolické komplikace.

Příčiny hypertrofie LKS



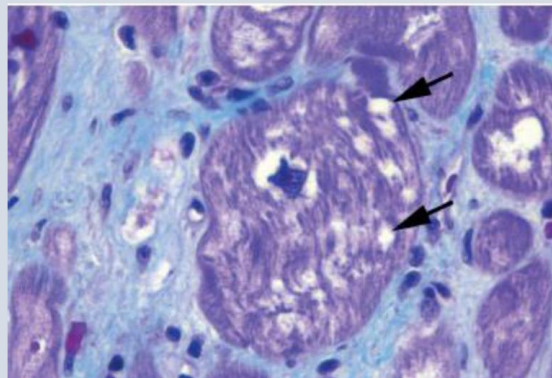
Hypertrofie
kardiomyocytů

A) **HT, valvulopatie**, obezita,
léky; koncentrická LVH
B) Atletické srdce: LVH
C) HKMP: asymetrická LVH



Infiltrace
intersticia

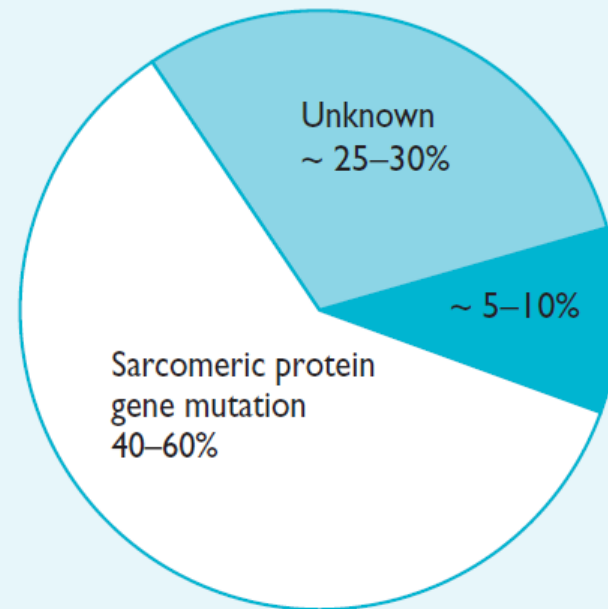
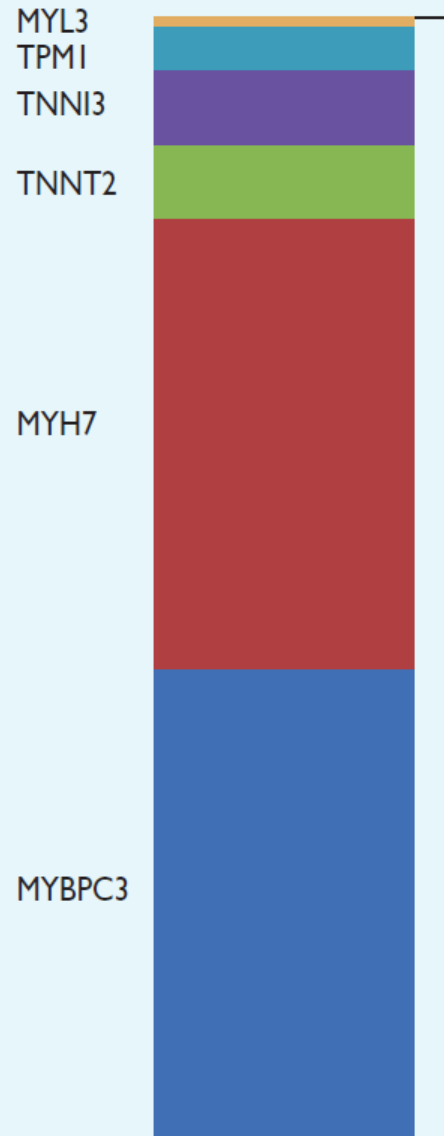
Amyloidóza: difuzní ztluštění
stěn obou komor, IAS,
chlopně; AL- nízká voltáž
EKG, těžká PSI



Střádání
metabolitů
intracelulárně

A) Glykogenózy: m.Pompe
B) Lysozomální choroby:
m.Fabry, Danonova nemoc
C) Mukopolysacharidózy

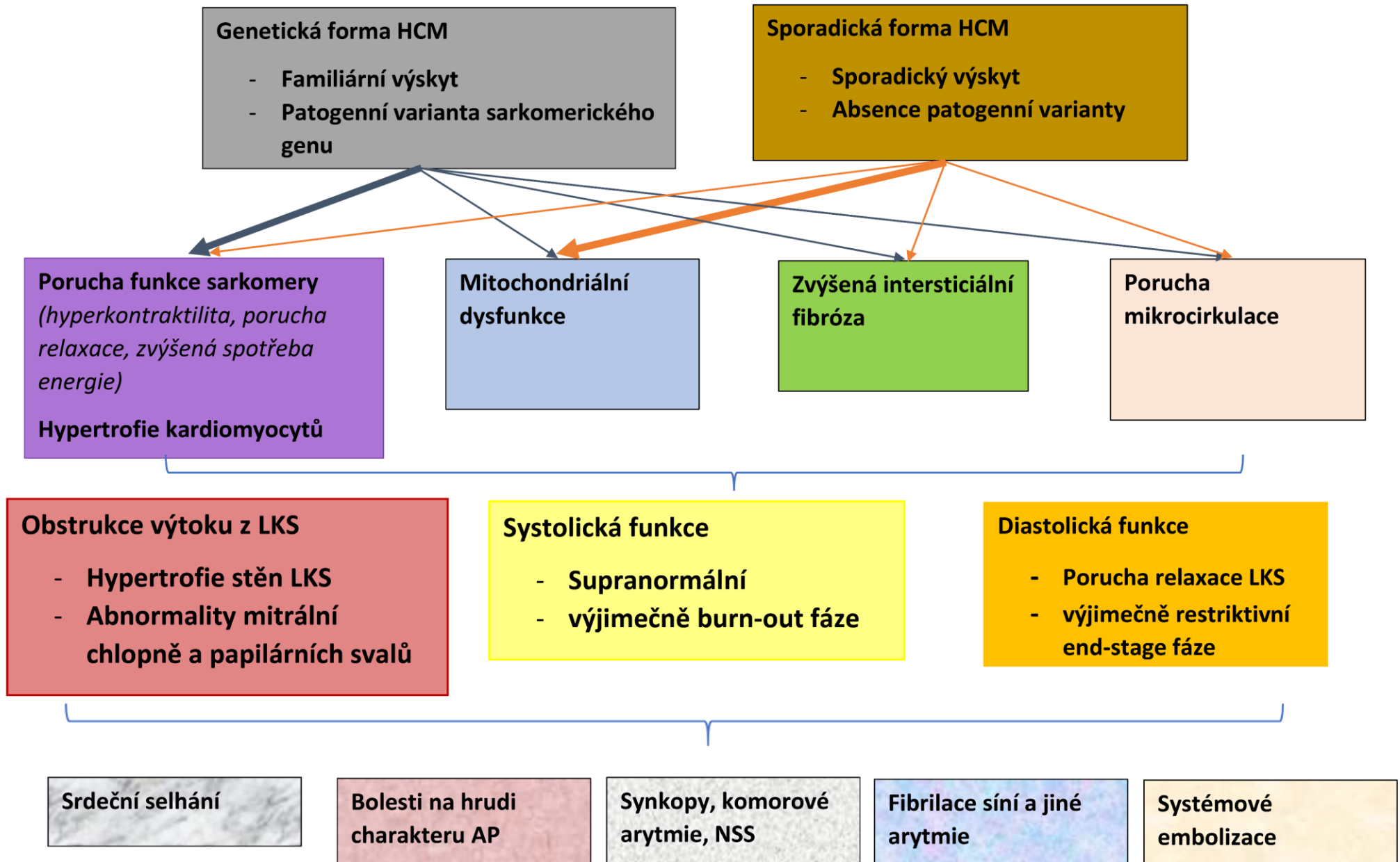
Etiologie HKMP



Other genetic and non-genetic causes

- **Inborn errors of metabolism**
 - Glycogen storage diseases:
 - Pompe
 - Danon
 - AMP-Kinase (PRKAG2)
 - Carnitine disorders
 - Lysosomal storage diseases
 - Anderson-Fabry
- **Neuromuscular diseases**
 - Friedreich's ataxia
 - FHLI
- **Mitochondrial diseases**
 - MELAS
 - MERFF
- **Malformation Syndromes**
 - Noonan
 - LEOPARD
 - Costello
 - CFC
- **Amyloidosis**
 - Familial ATTR
 - Wild type TTR (senile)
 - AL amyloidosis
- **Newborn of diabetic mother**
- **Drug-induced**
 - Tacrolimus
 - Hydroxychloroquine
 - Steroids

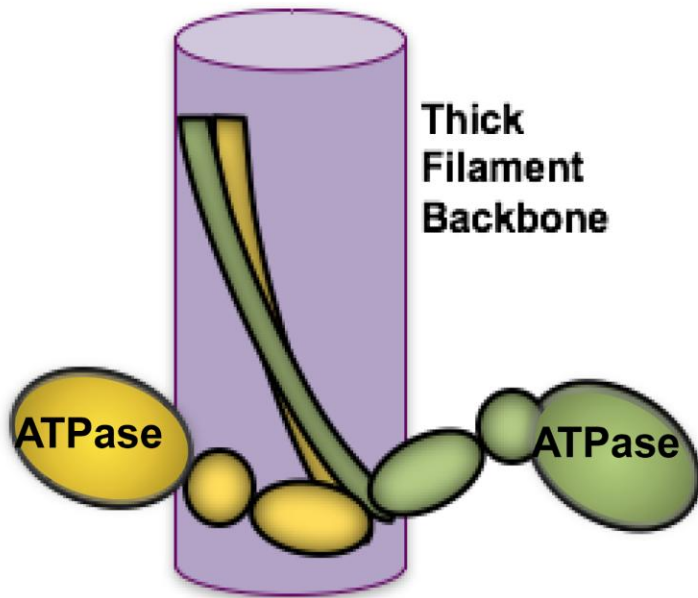
Patogeneze HCM



Konformace myosinu během srdečního cyklu ve vztahu ke konzumpci energie

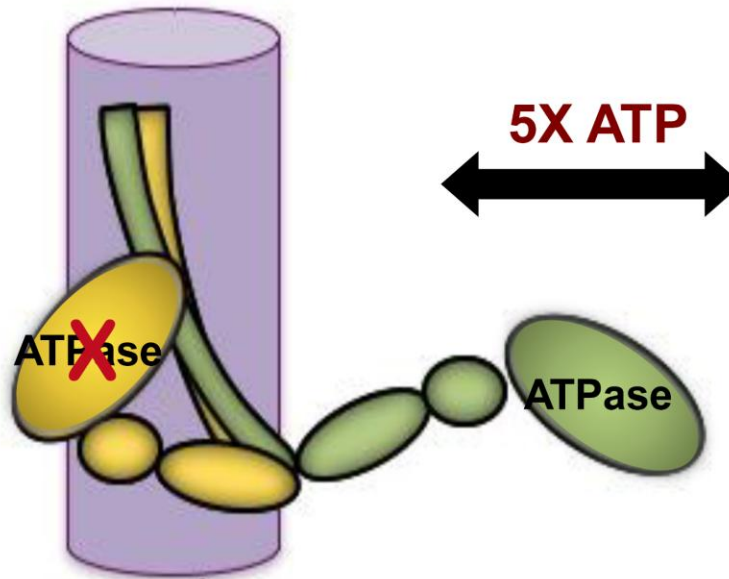
Two States of Sarcomere Relaxation & Energetics

Contraction



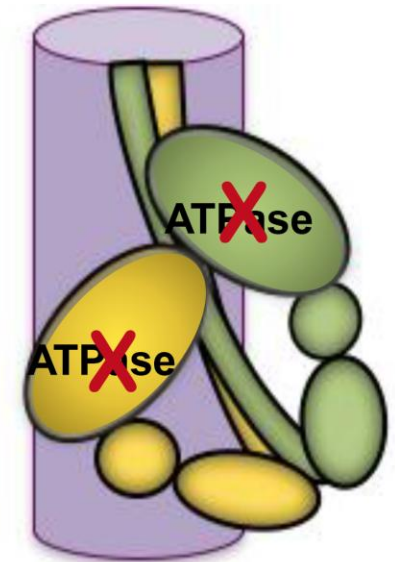
Two ATPase Active

Disordered Relaxation
(DRX)



One ATPase Inhibited

Super Relaxation
(SRX)

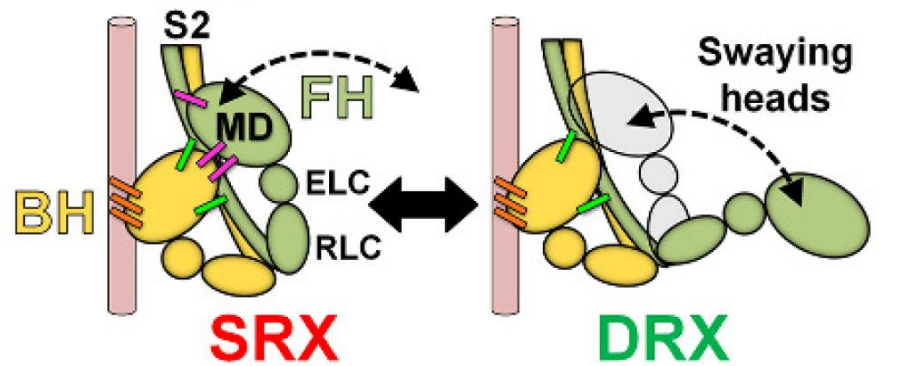


Two ATPases Inhibited

Energy Consumption

Dysfunkce sarkomery u genetických forem HCM

A Healthy MD and IHM



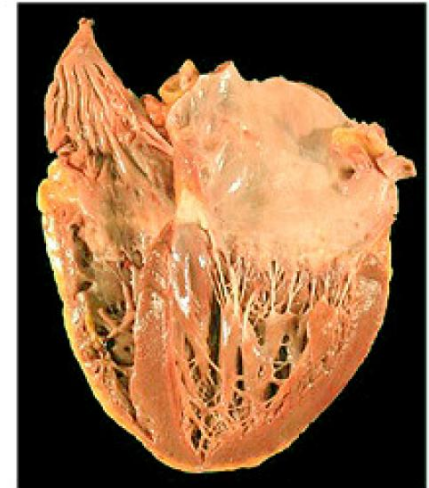
- ▬ IHM priming intra-molecular interactions (g, f)
- ▬ IHM anchoring inter-molecular interactions (h, j, i)
- ▬ IHM stabilizing intra-molecular interactions (e, d, a)

MD

- ATPase
- Actin-binding
- Converter
- Force

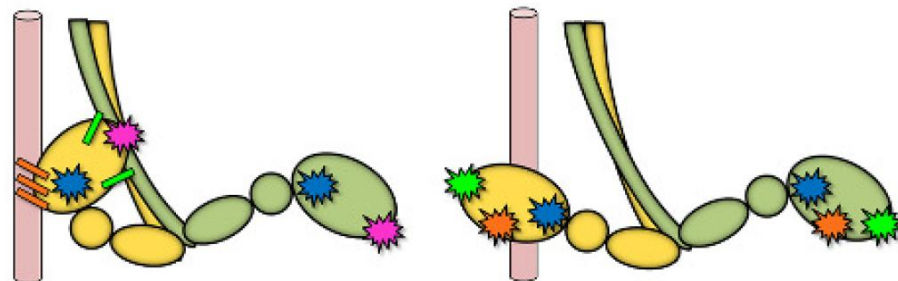
IHM

- Physiologic **SRX** : **DRX**
- Swaying
- Force Potentiation
- SRX
- Relaxation
- Energy conservation



Normal Contraction
Normal Relaxation
Homeostatic Metabolism

B HCM



- ★ ↑ MD Function
- ★ ↓ IHM Priming
- ★ ↓ IHM Anchoring
- ★ ↓ IHM Stabilization

Mutated MD

- ↑ ATPase
- ↑ Actin-binding
- ↑ Converter
- ⤴ Force

Mutated IHM

- SRX** << **DRX**
- ↑ Swaying
- ⤴ Force Potentiation
- ↓ SRX
- ⤴ Relaxation
- ↑ Energy consumption



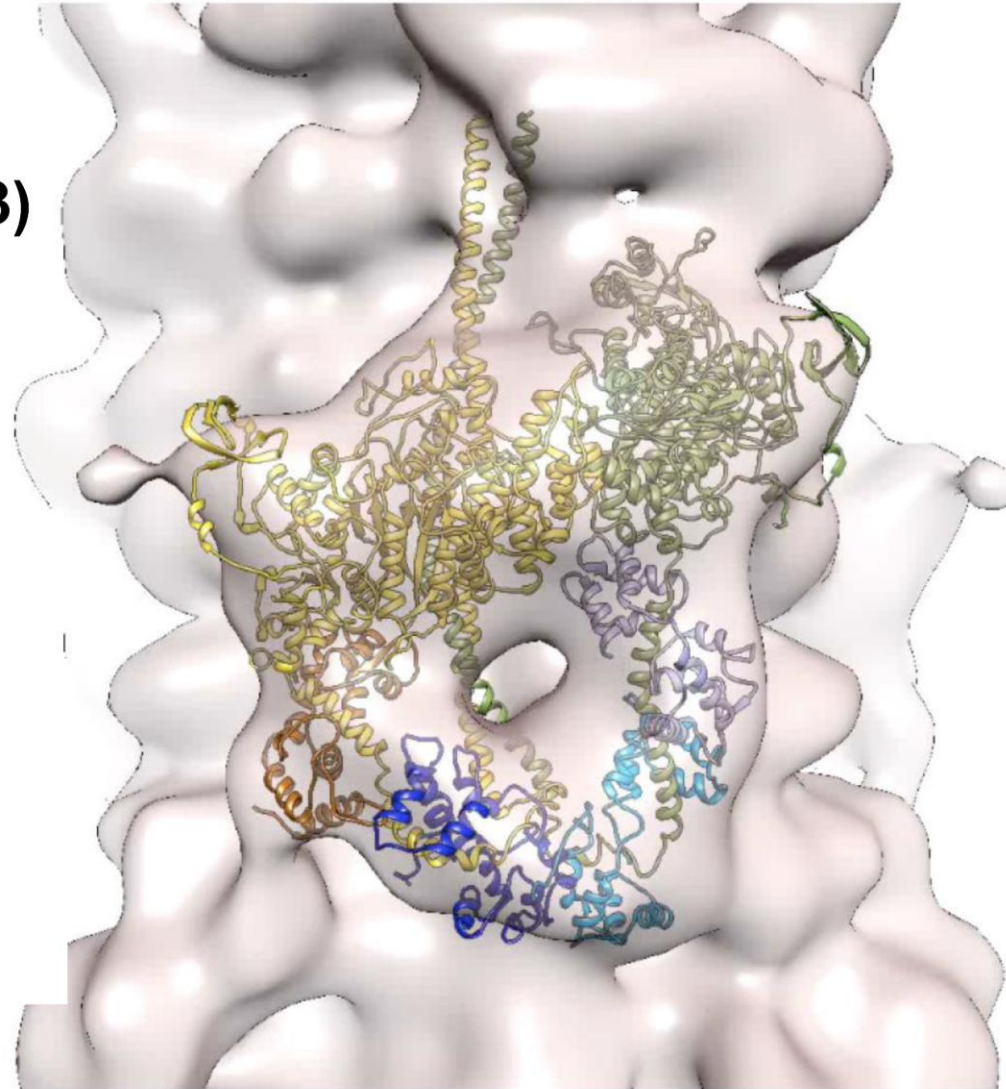
Hyperdynamic Contraction
Reduced Relaxation
Increased Metabolism

HCM Mutations: Clustered in Residues Participating in SRX and DRX Conformations

HCM Mutations in 6000 Patients:

78% alter Interacting Residues
(vs. Chance, $p=5.25e-13$)

71% alter Residue Charge



Inhibice ATPasy srdečního myosinu u myšního modelu HCM

Science. 2016 February 5; 351(6273): 617–621.

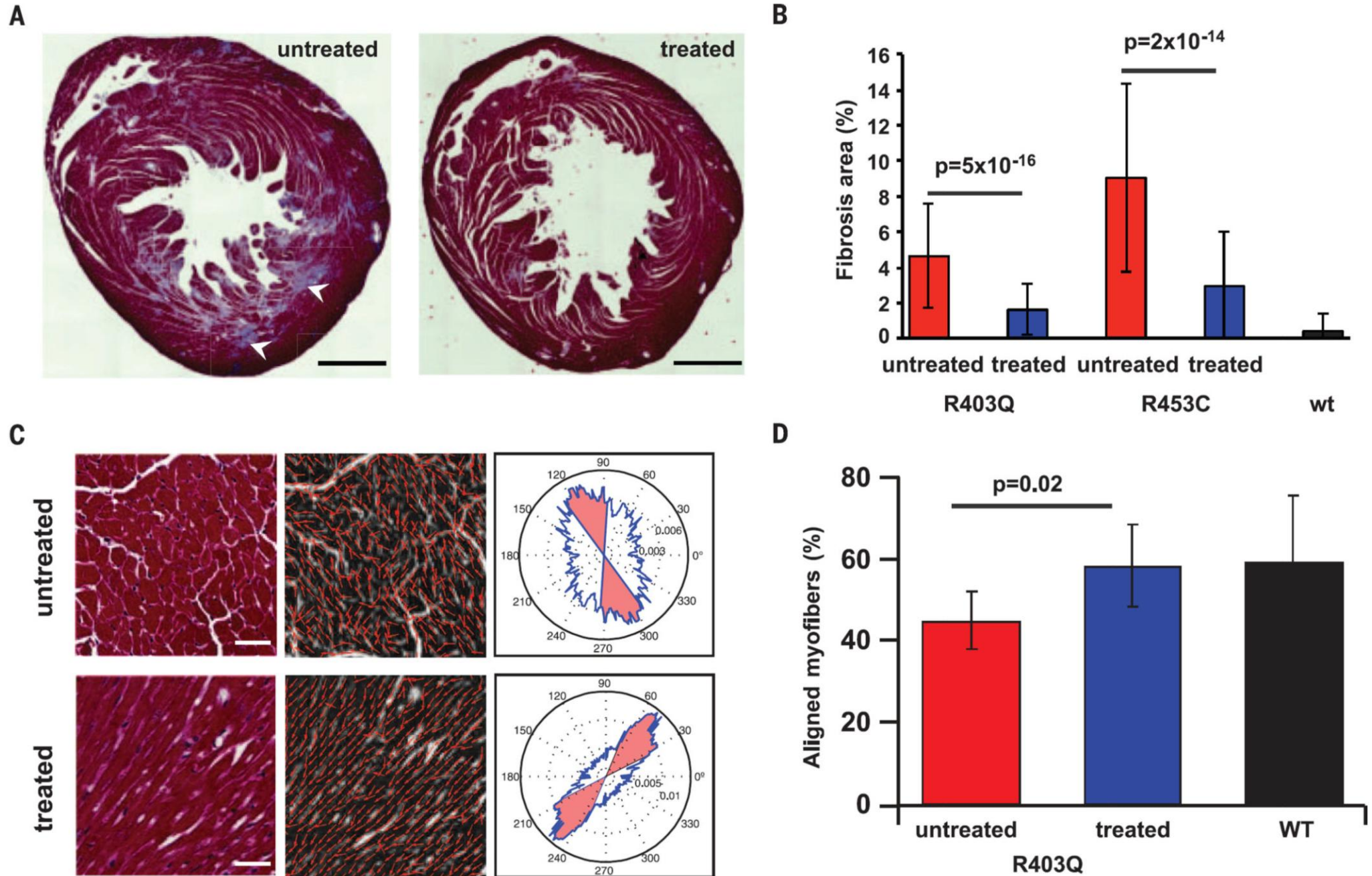


Fig. 3. MYK-461 reduces the development of myocardial disarray and fibrosis in mouse models of HCM

Inhibice ATPasy srdečního myosinu v tkáňových kulturách myších KMC a na lidských iPSC

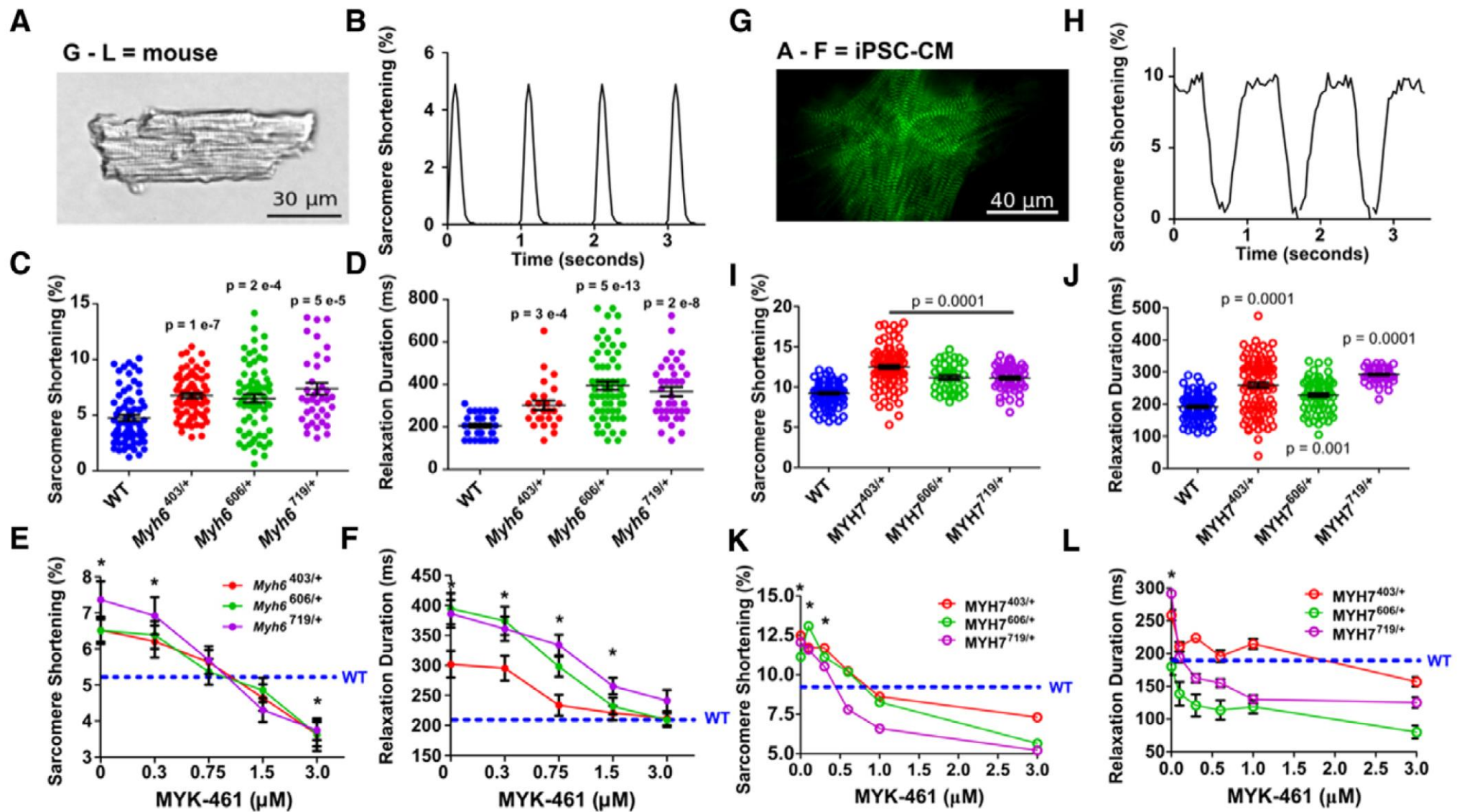
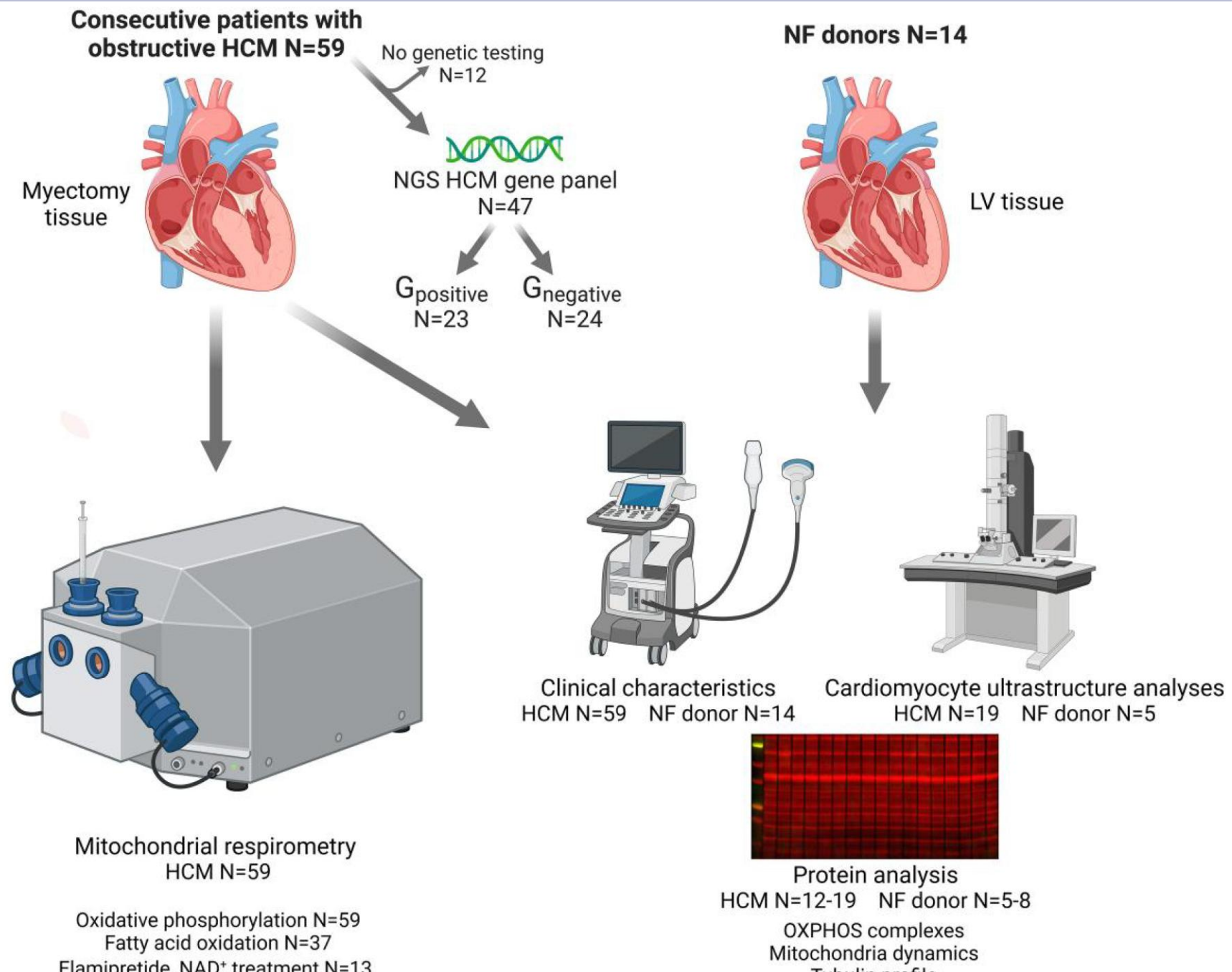


Figure 3. Pathogenic hypertrophic cardiomyopathy myosin variants in mouse cardiomyocytes and iPSC-CMs exhibit hypercontractility and abnormal relaxation that is normalized by interacting heads motif restabilization with MYK-461.

Mitochondriální dysfunkce u genotyp-negativních forem HCM

European Heart Journal (2023) **44**, 1170–1185

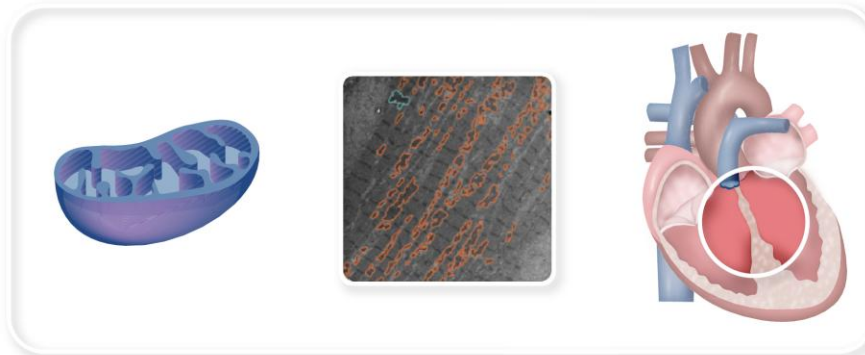


Mitochondrial dysfunction in human hypertrophic cardiomyopathy is linked to cardiomyocyte architecture disruption and corrected by improving NADH-driven mitochondrial respiration

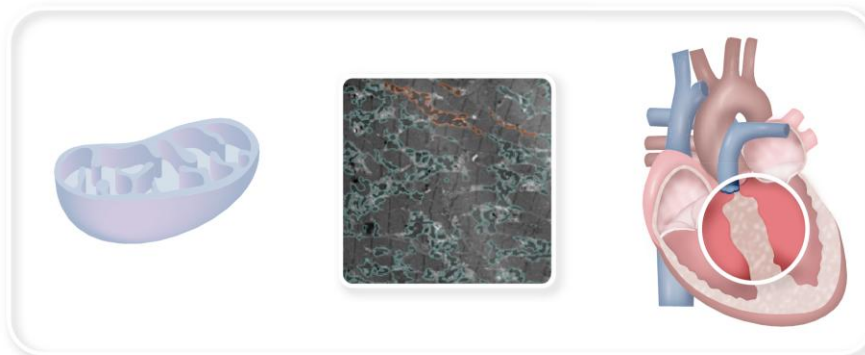
Nollet EE, Duursma I, Rozenbaum A, Eggelbusch M, Wüst RCI, Schoonvelde SAC, Michels M, Jansen M, van der Wel NN, Bedi KC, Margulies KB, Nirschl J, Kuster DWD, van der Velden J.

European Heart Journal (2023) **44**, 1170–1185

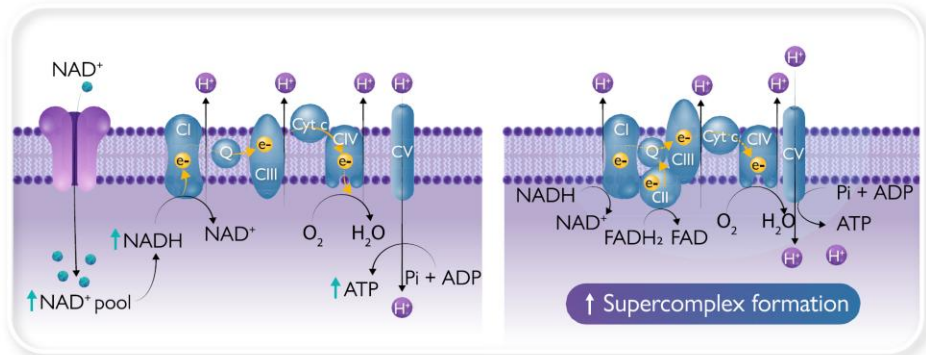
Variable mitochondrial function in HCM



Impaired mitochondrial function Cardiomyocyte architecture disruption Septal thickness in genotype-negative HCM

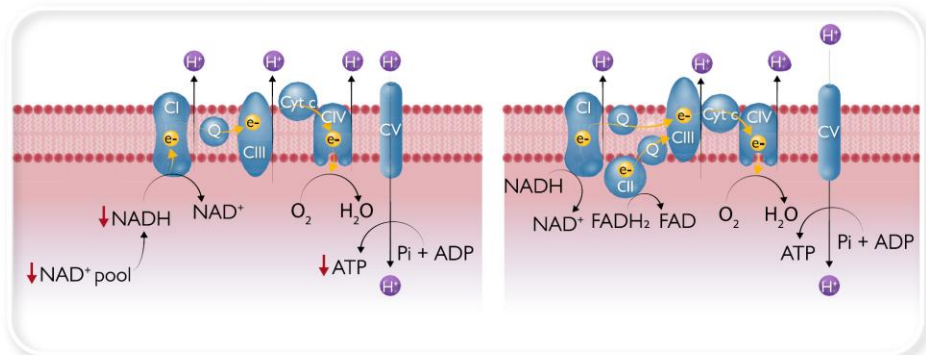


Therapeutic strategies to improve mitochondrial function



Raising NAD⁺ levels

Elamipretide

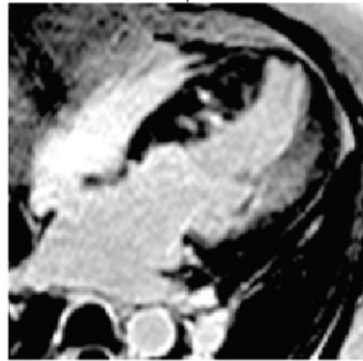


Rozdíly mezi genotyp-positivní a genotyp-negativní formou HCM při CMR

2,755 Hypertrophic Cardiomyopathy Patients
44 sites
6 countries
North America and Europe

2 broad, relatively distinct populations

36%



Sarcomere mutation (+)
More Likely:

Reverse septal curvature morphology
More late gadolinium enhancement
and interstitial fibrosis
No significant left ventricular outflow
tract obstruction

64%

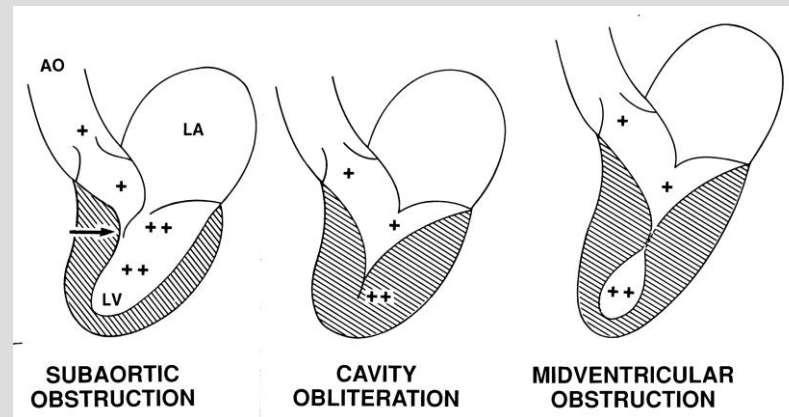


Sarcomere mutation (-)
More Likely:

Isolated basal septal morphology
Less late gadolinium enhancement
and interstitial fibrosis
More left ventricular outflow
tract obstruction

Mechanismy obstrukce výtoku z LKS u HCM

- **Lokalizace obstrukce:** výtokový trakt (LVOT), midventrikulárně, popř. intraventrikulárně.



Circulation. 1995 Oct 1;92(7):1680-92.

- **Podmínky pro vznik obstrukce:**

1. Rozsah a distribuce hypertrofie LKS
2. Anatomie mitrální chlopně
3. Anatomie papilárních svalů
4. Aktuální hodnoty preloadu a afterloadu

Závěr 1:

- Genetickou etiologii HCM můžeme vystopovat u cca 40% nemocných HCM.

- U genetických forem HCM jsou dominantním mechanismem etiopatogeneze hyperkontraktilita sarkomery a porucha relaxace při depleci superrelaxované formy beta-isoformy těžkého řetězce myosinu.

- Tyto změny vedou k zvýšené spotřebě energie a pravděpodobně přispívají k progresi hypertrofie LKS.

- Inhibice ATPasy srdečního myosinu koriguje hyperkontraktilitu a porušenou relaxaci u tkáňových a zvířecích modelů genetických forem HCM.

Závěr 2:

- U genotyp-negativních jedinců obstrukční formou HCM byla recentně ve vzorcích z myektomie identifikována **významná mitochondriální dysfunkce**, která korelovala s tíží ultrastrukturálních změn v myokardu a tloušťkou IVS na zobrazovacích metodách.
- Odlišnou patofyziologii genotyp-pozitivní a genotyp-negativní HCM lze podchytit také při MR srdce. Pro **genotyp-pozitivní formu** jsou typické reverzní vyklenování IVS do dutiny LKS, výraznější známky fibrózy a méně častá obstrukce LVOT.

Děkuji Vám za pozornost!

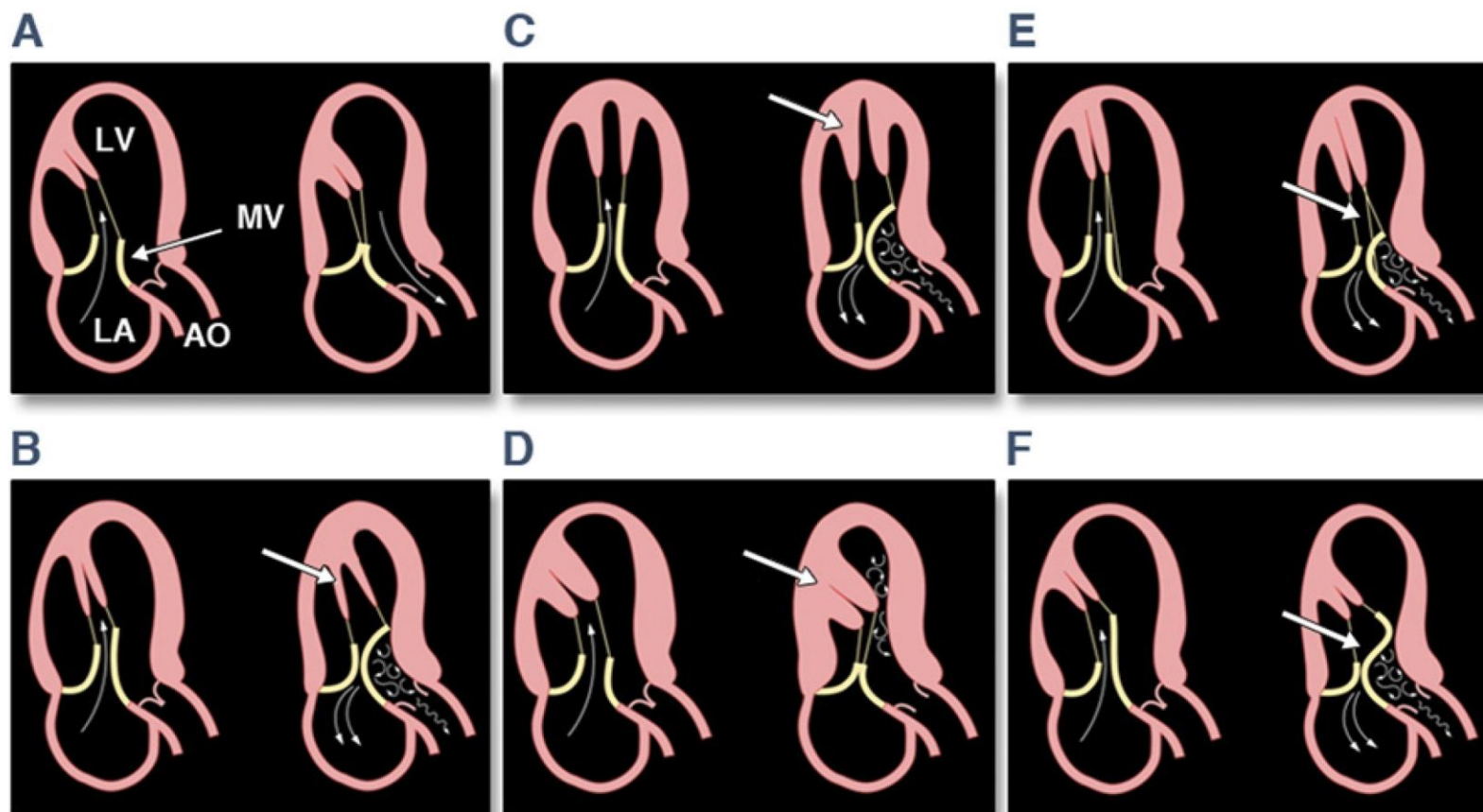


Figure 7. Schematic Diagram of the Common Variations in Papillary Muscle Anatomy in HCM

Schematic diagram of the common variations in papillary muscle anatomy in HCM (arrows). The left image represents the myocardium during diastole, the right image represents systole. (A) Normal papillary muscle orientation; (B) bifid papillary muscles; (C) apical displacement of the papillary muscles; (D) hypertrophied papillary muscles with mainly mid-cavity obstruction during systole; (E) abnormal chordal attachment to the mid-portion of the mitral valve (MV); and (F) elongated anterior MV leaflet. See [Online Video 2](#). Ao = aorta; LA = left atrium; LV = left ventricle; other abbreviation as in Figure 1.