FN MOTOL

KARDIOLOGICKÁ KLINIKA
2. LF UK a FN MOTOL

Genetické vyšetření u hypertrofické kardiomyopatie

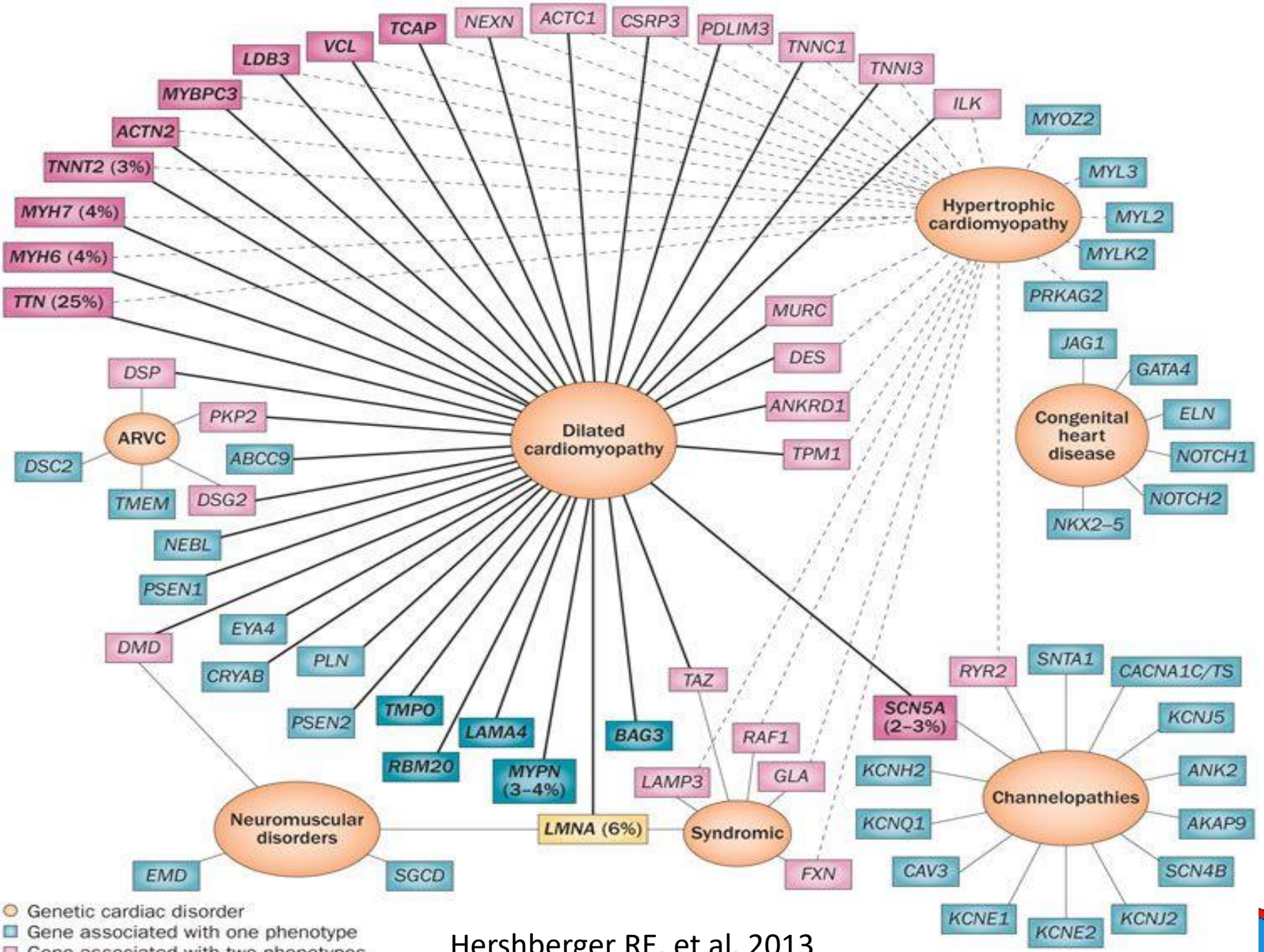
Jiří Bonaventura

Kardiologická klinika 2. LF UK a FN Motol

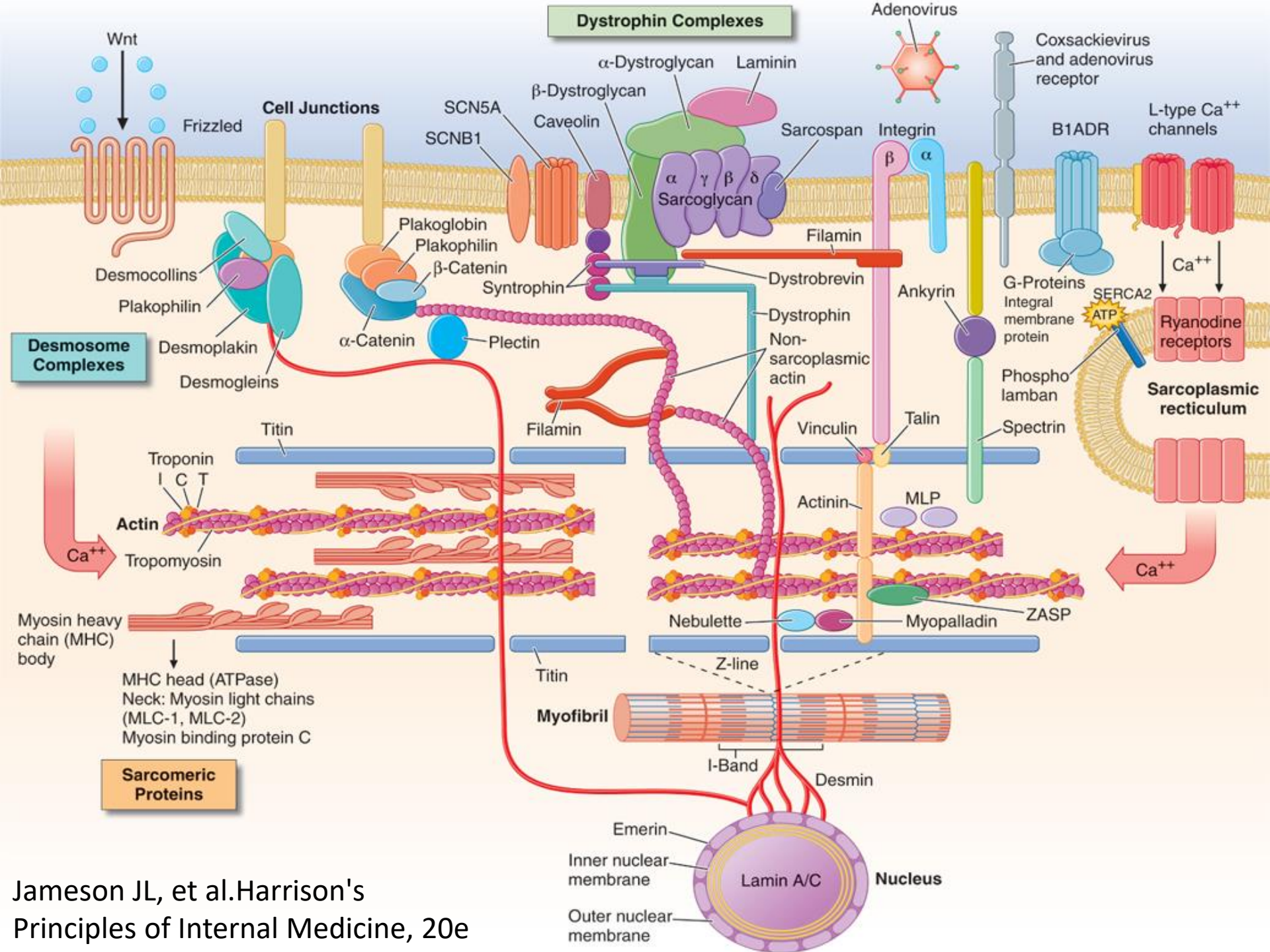
Kardio 35 - IV. sjezd českých a slovenských mladých kardiologů Kurdějov, 27.9.2019

Genetika kardiomyopatií

- Některé kardiomyopatie jsou monogenně podmíněná onemocnění
- Dedičnost může být AD, AR, X-vázaná i mitochondriální
- Velká genotypová variabilita - desítky genů, tisíce mutací
- Mutace v genech pro proteiny kardiomyocytů (sarkolemma, iontové kanály, kotvící proteiny, myofibrily, jaderný obal, mitochondrie, sarkoplasmatické retikulum)
- Výtěžnost genetického vyšetření je variabilní
- Genetické poradenství
- Prognostický význam?



Hershberger RE, et al. 2013



Jameson JL, et al.Harrison's Principles of Internal Medicine, 20e

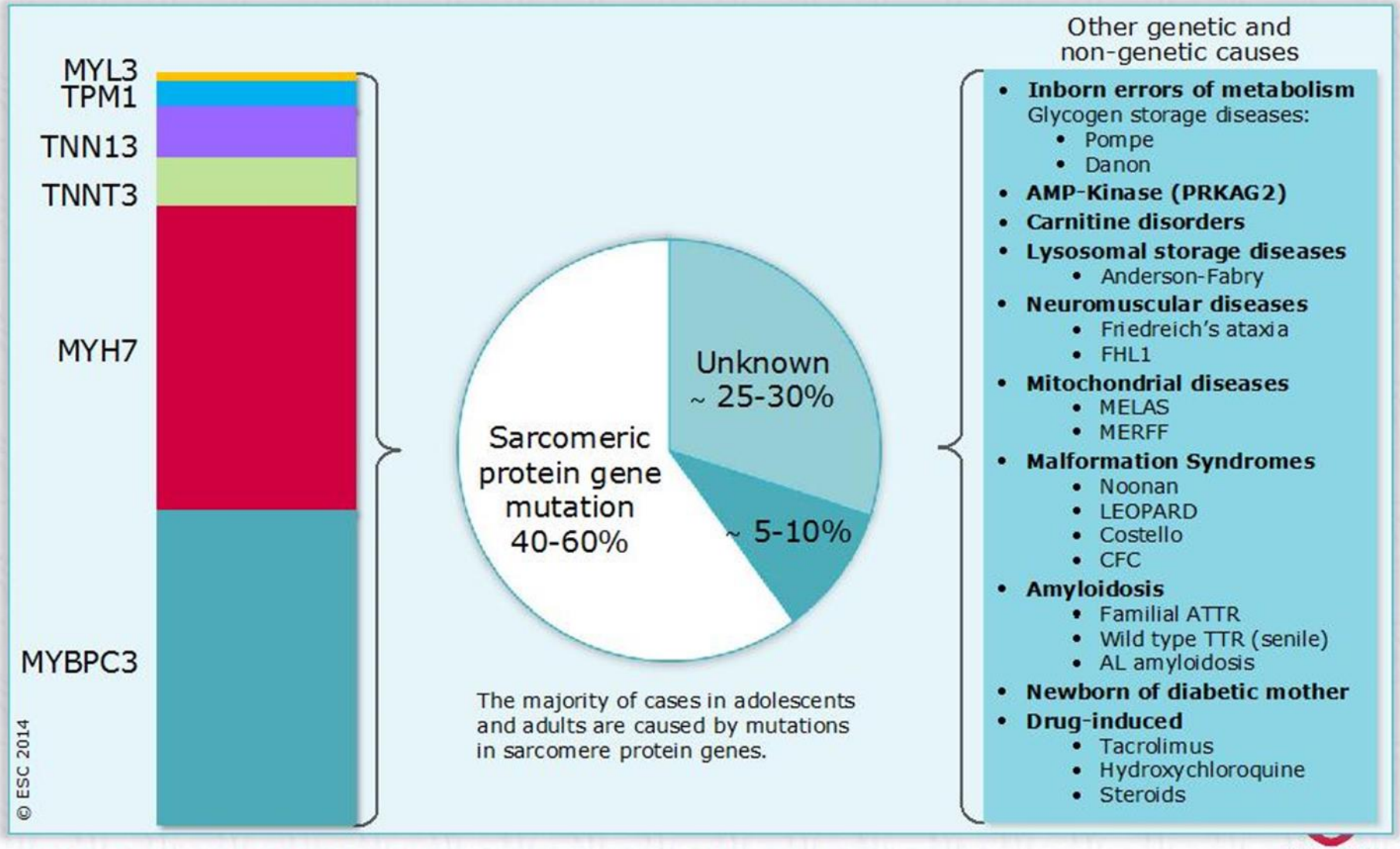
Genetika HCM

- Autosomálně dominantní dědičnost – tj. 50% riziko pro příbuzné 1. stupně?
- Mutace genů pro sarkomerické proteiny – 20-40% pacientů
- Velká genotypová i fenotypová heterogenita
  - Více než 2000 mutací v 26 genech

- ESC: 5-10 % nemocných tvoří metabolické a neuromuskulární choroby, jiné gen. abnormality a syndromy i negenetické příčiny

www.omim.org

Diverse aetiology of hypertrophic cardiomyopathy



www.escardio.org/guidelines European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

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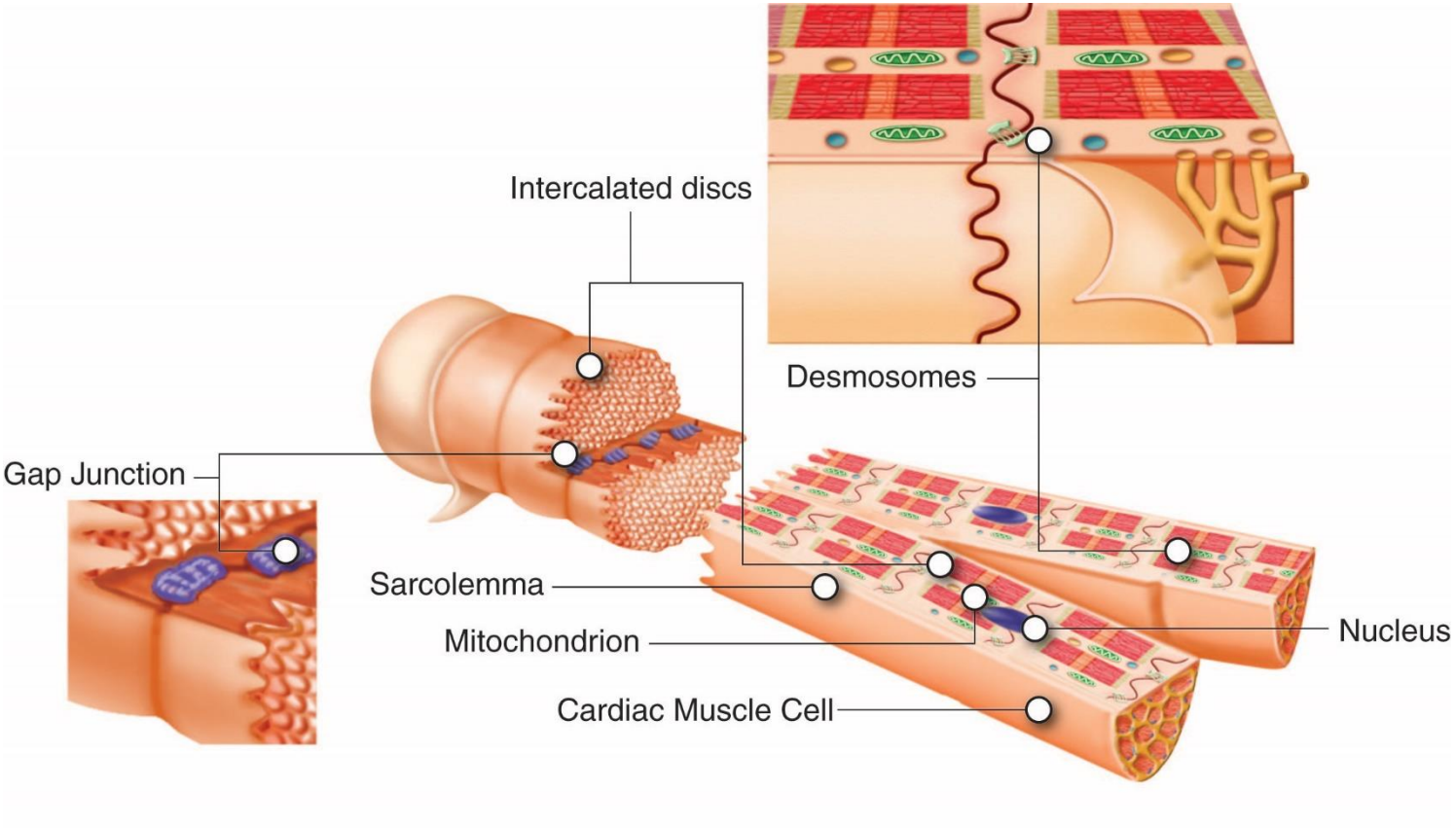
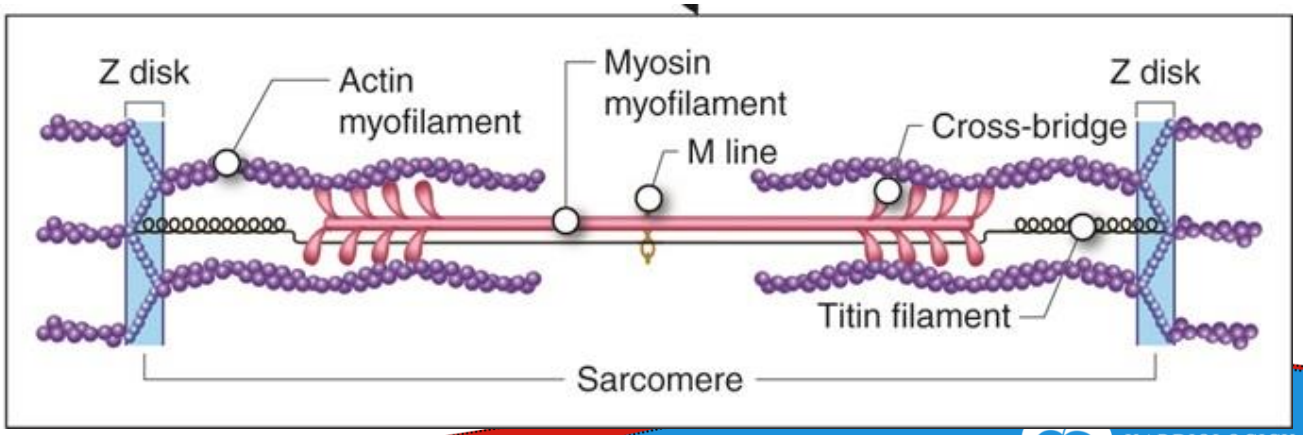
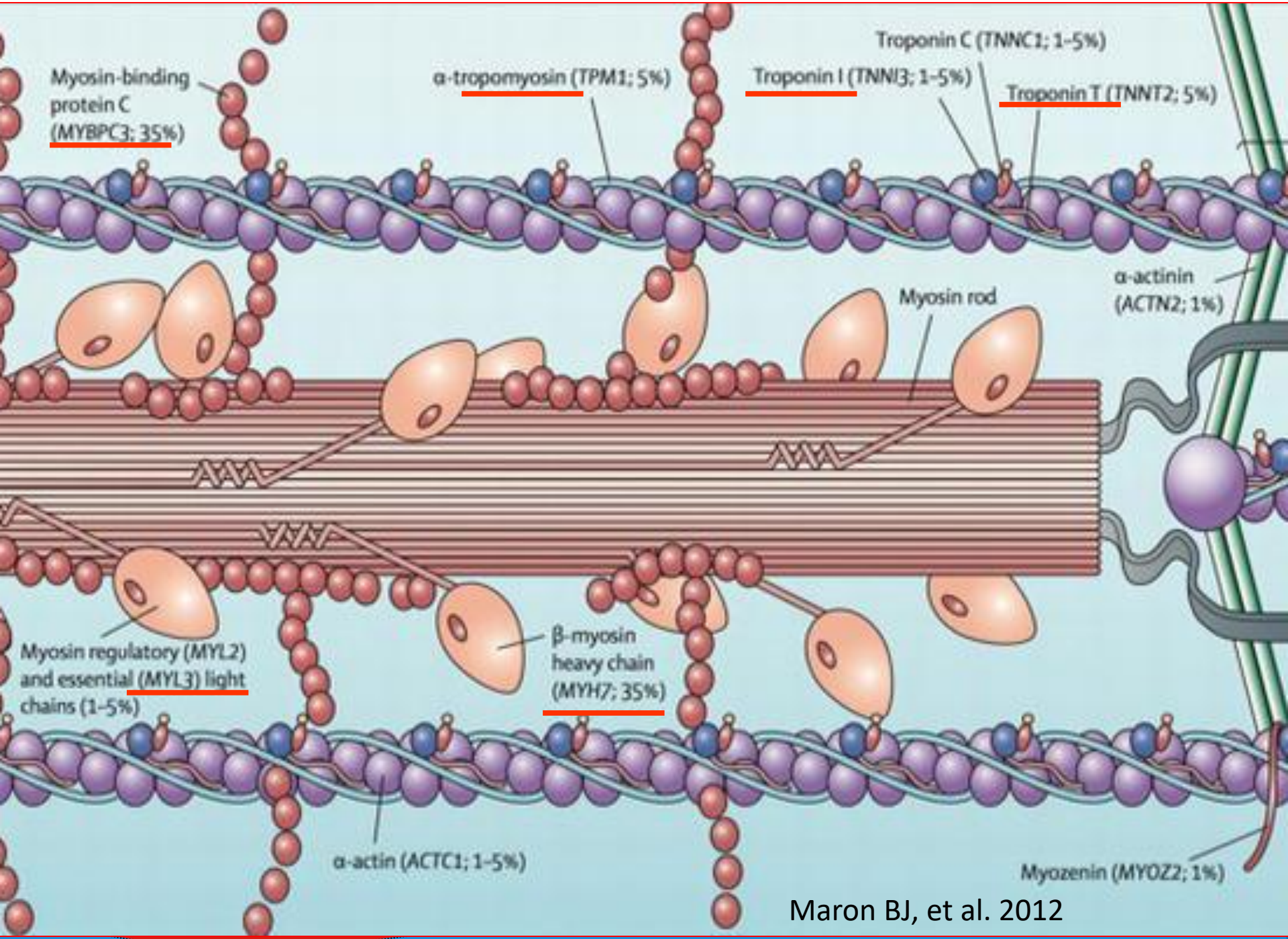
Elliot P, et al. 2014


Intercalated discs
Desmosomes
Gap Junction
Sarcolemma
Mitochondrion
Nucleus
Cardiac Muscle Cell


Z disk
Actin myofilament
Myosin myofilament
M line
Cross-bridge
Z disk
Titin filament
Sarcomere



Maron BJ, et al. 2012

Examples of signs and symptoms suggestive of specific diagnoses

Symptom/sign	Diagnosis
Learning difficulties, mental retardation	• Mitochondrial diseases • Noonan/LEOPARD/Costello syndrome • Danon disease
Sensorineural deafness	• Mitochondrial diseases (particularly with diabetes) • Anderson-Fabry disease • LEOPARD syndrome
Visual impairment	• Mitochondrial diseases (retinal disease, optic nerve atrophy) • TTR-related amyloidosis (cotton wool type vitreous opacities) • Danon disease (retinitis pigmentosa) • Anderson-Fabry disease (cataracts, corneal opacities)

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

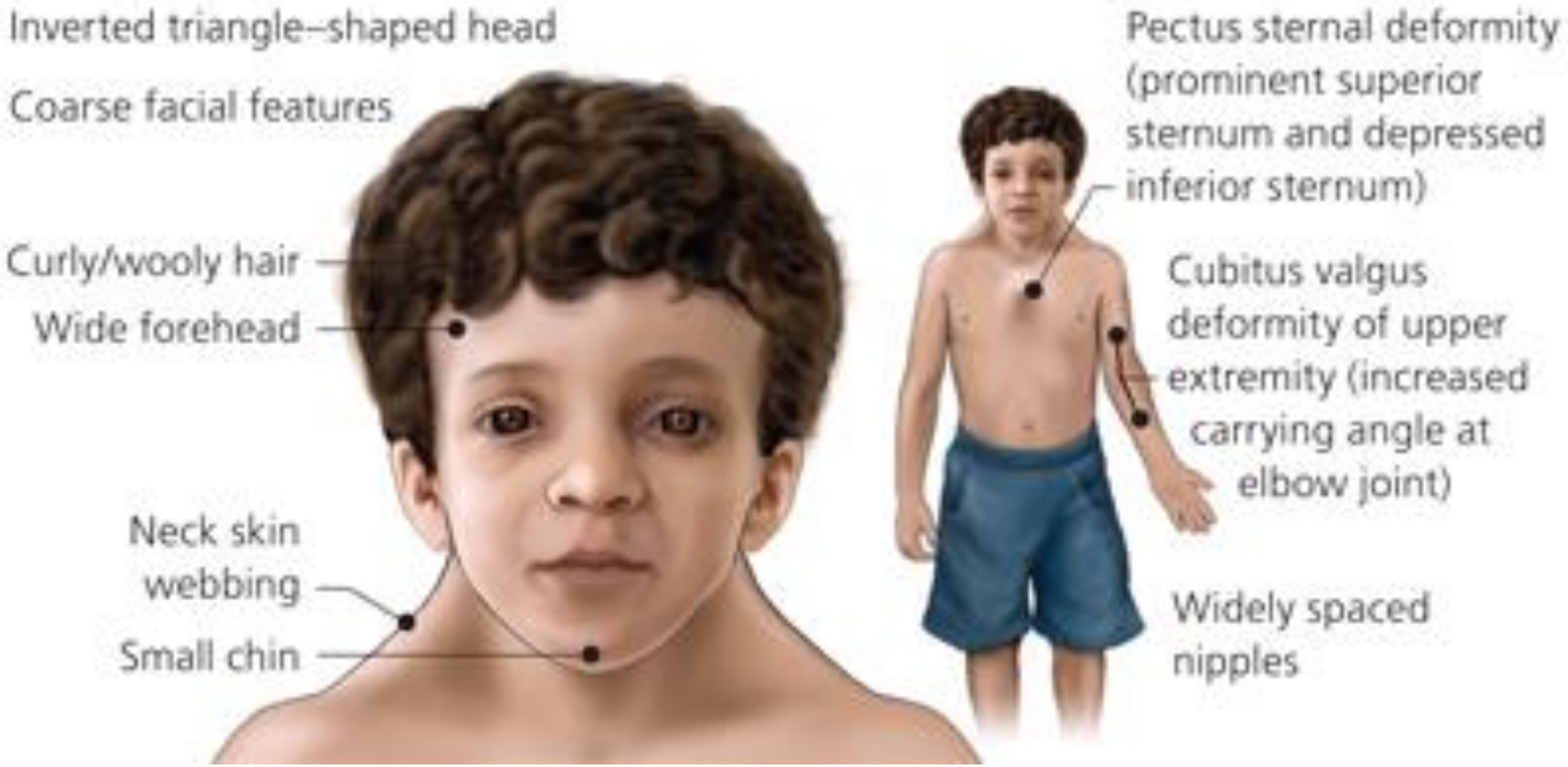
Examples of signs and symptoms suggestive of specific diagnoses *(Cont.)*

Symptom/sign	Diagnosis
Gait disturbance	• Friedreich's ataxia
Paraesthesia/sensory abnormalities/neuropathic pain	• Amyloidosis • Anderson-Fabry disease
Carpal tunnel syndrome	• TTR-related amyloidosis (especially when bilateral and in male patients)
Muscle weakness	• Mitochondrial diseases • Glycogen storage disorders • FHL1 mutations • Friedreich's ataxia
Palpebral ptosis	• Mitochondrial diseases • Noonan/LEOPARD syndrome • Myotonic dystrophy
Lentigines/café au lait spots	• LEOPARD/Noonan syndrome
Angiokeratomata, hypohidrosis	• Anderson-Fabry disease

FHL1 = four and a half LIM domains 1; LEOPARD = lentigines, ECG abnormalities,ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and sensorineural deafness; TTR = transthyretin.

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Noonan syndrome



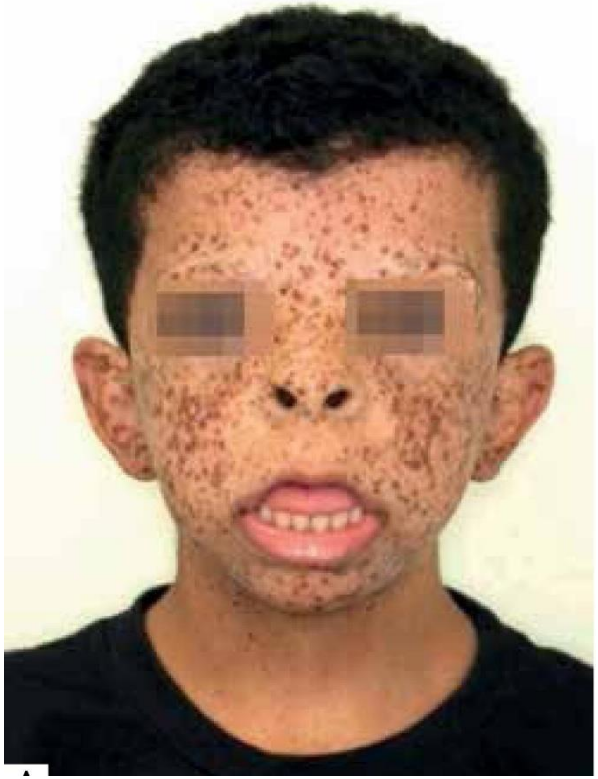
1:1000 – 1:2500

LEOPARD syndrome

=

Noonan syndrome with multiple lentigines (NSML)

Lentigines
Electrocardiographic conduction abnorm.
Ocular hypertelorism
Pulmonary stenosis
Abnormal genitalia
Retarded growth
Deafness



Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants

Finding	Comment
Short PR interval/ pre-excitation	Pre-excitation is a common feature of storage diseases (Pompe, PRKAG2, and Danon) and mitochondrial disorders (MELAS, MERFF). A short PR interval without pre-excitation is seen in Anderson-Fabry disease.
AV block	Progressive atrioventricular conduction delay is common in mitochondrial disorders, some storage diseases (including Anderson-Fabry disease), amyloidosis, desminopathies and in patients with PRKAG2 mutations.
Extreme LVH (Sokolow score ≥50)	Extremely large QRS voltage is typical of storage diseases such as Pompe and Danon disease, but can be caused by pre-excitation alone.
Low QRS voltage (or normal voltages despite increased LV wall thickness)	Low QRS voltage in the absence of pericardial effusion, obesity and lung disease is rare in HCM (limited to cases with end-stage evolution) but is found in up to 50% of patients with AL amyloidosis and 20% with TTR amyloidosis. Differential diagnosis between HCM and cardiac amyloidosis is aided by measuring the ratio between QRS voltages and LV wall thickness.

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Echocardiographic features that suggest specific aetiologies

Finding	Specific diseases to be considered
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion.	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2-D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

PRKAG2 = gamma-2 subunit of the adenosine monophosphate-activated protein kinase;

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Genetika HCM

- Neúplná penetrance, variabilní expresivita
  - 55% mezi 10. a 29. rokem
  - 75% mezi 30. a 49. rokem
  - 95% po 50.roce věku
  - Pravděpodobně muži > ženy
- Vztah s jinými kardiomyopatiemi – mutace stejných genů
- Modifikace fenotypu genetickými (siRNA, miRNA…) a negenetickými faktory?

Michels M et al., Eur Heart J. 2009

Genetic testing in probands

Recommendations	Class	Level
Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.	I	B
It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.	I	C
In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.	I	B
Genetic testing in patients with a borderline[a] diagnosis of HCM should be performed only after detailed assessment by specialist teams.	IIa	C
Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.	IIa	C

[a]Borderline: left ventricular wall thickness 12 – 13 mm in adults; left ventricular hypertrophy in the presence of hypertension, athletic training, valve disease.

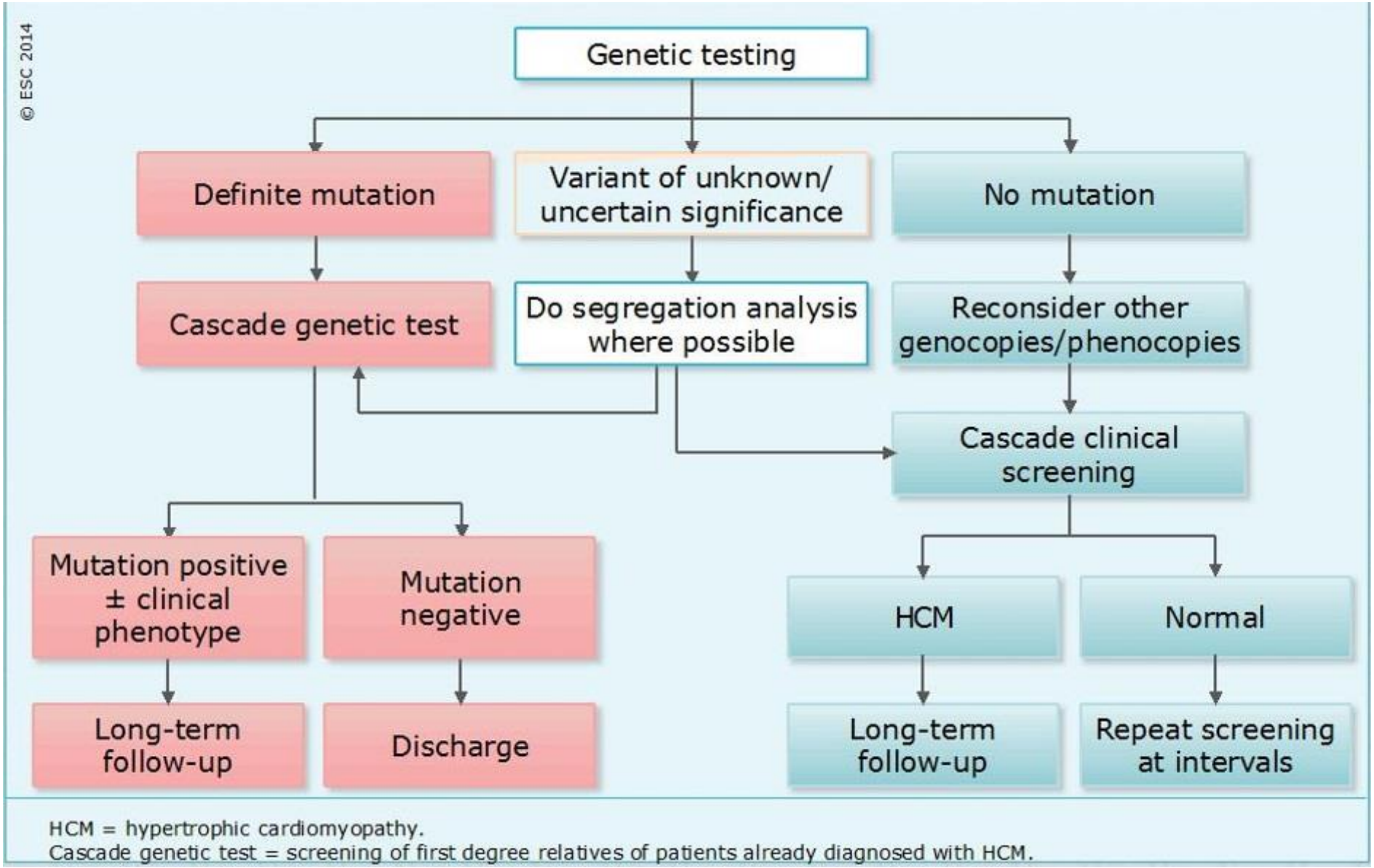
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Genetic and clinical testing of adult relatives

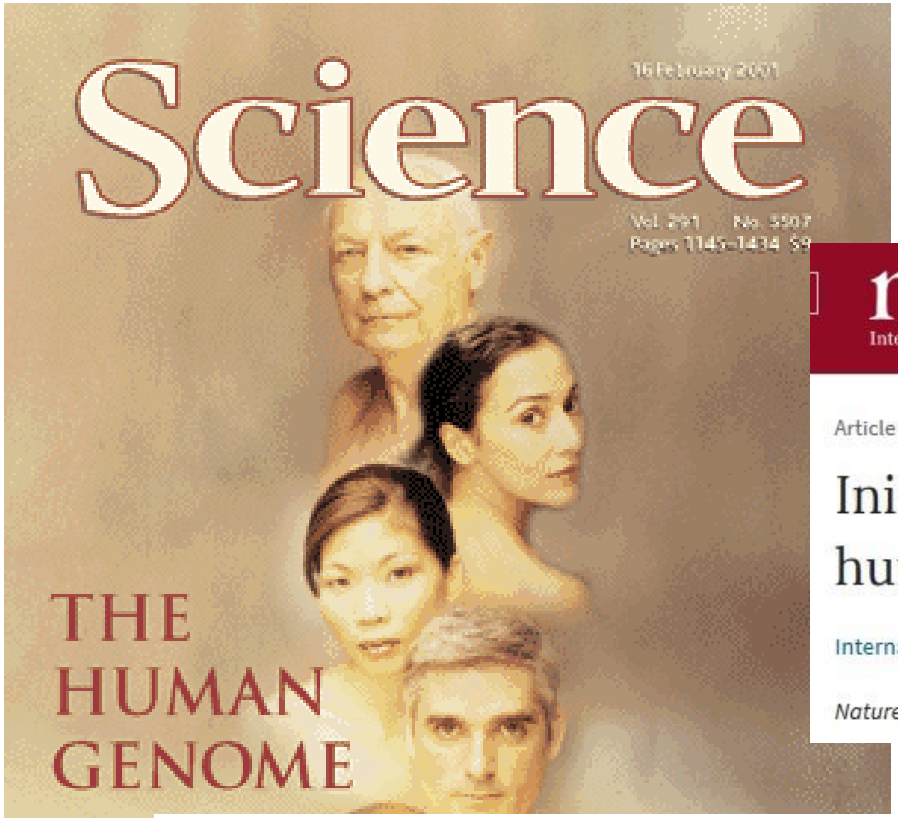
Recommendations	Class	Level
Cascade genetic screening, after pre-test counselling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation.	I	B
Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband.	I	C
First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.	IIa	B
When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2-5 years (or 6-12 monthly if non-diagnostic abnormalities are present).	IIa	C

Proband = usually the first family member to be diagnosed with the condition.

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284


© ESC 2014
Genetic testing
Definite mutation
Variant of unknown/ uncertain significance
No mutation
Cascade genetic test
Do segregation analysis where possible
Reconsider other genocopies/phenocopies
Cascade clinical screening
Mutation positive ± clinical phenotype
Mutation negative
HCM
Normal
Long-term follow-up
Discharge
Long-term follow-up
Repeat screening at intervals
HCM = hypertrophic cardiomyopathy.
Cascade genetic test = screening of first degree relatives of patients already diagnosed with HCM.

Human Genome Project



nature
International journal of science

Article | Published: 15 February 2001

Initial sequencing and analysis of the human genome

International Human Genome Sequencing Consortium

Nature **409**, 860–921 (15 February 2001) | Download Citation

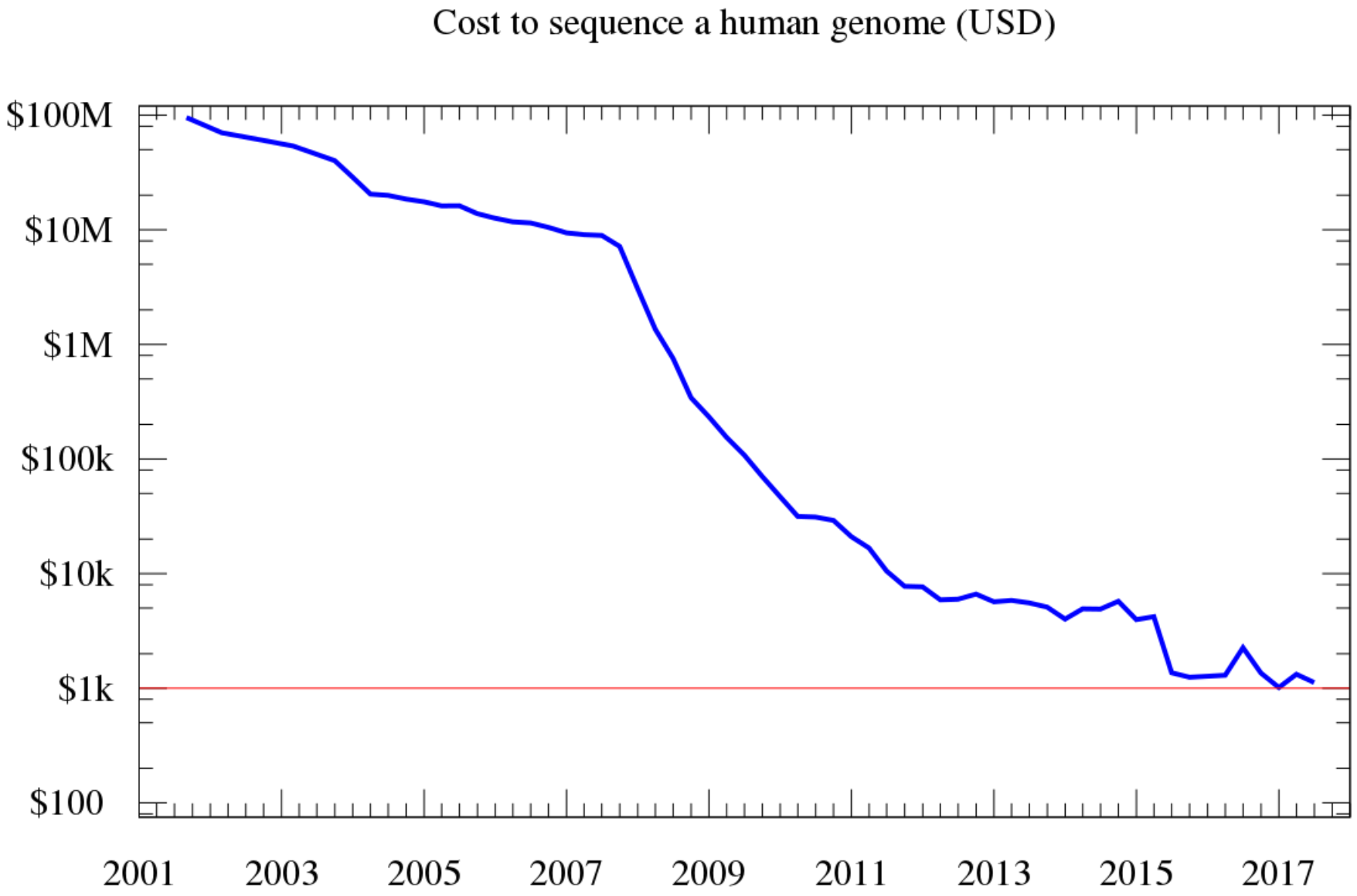
The Sequence of the Human Genome

J. Craig Venter[1,*], Mark D. Adams[1], Eugene W. Myers[1], Peter W. Li[1], Richard J. Mural[1], Granger G. Sutton[1], Hamilton O. S...

+ See all authors and affiliations

Science 16 Feb 2001:
Vol. 291, Issue 5507, pp. 1304-1351
DOI: 10.1126/science.1058040

Celera Genomics



National Human Genome Research Institute
https://www.genome.gov

Interpretace

- Metody NGS umožňují vyšetření velkého množství genů, ev. celého exomu či genomu
- Screening velkého množství genů má za následek nález velkého množství variant zatím nejasného významu (VUS - variants of unknown significance)
- Zatím nejsou žádná robustní data na vztahy genotypu a fenotypu
- Absence mutace v genu asociovaném s kardiomyopatií **ne**musí znamenat, že vyš. osoba s jistotou neonemocní (de novo mutace, VUS)
- Interpretace VUS kaskádovitě v rodinách s HCM

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192600

CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC, 1; CMH1

Alternative titles; symbols

CMH
VENTRICULAR HYPERTROPHY, HEREDITARY
ASYMMETRIC SEPTAL HYPERTROPHY; ASH
HYPERTROPHIC SUBAORTIC STENOSIS, IDIOPATHIC

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
3p25.3	Cardiomyopathy, familial hypertrophic	192600	AD	3	CAV3	601253
14q11.2	Cardiomyopathy, hypertrophic, 1	192600	AD	3	MYH7	160760
20q11.21	Cardiomyopathy, hypertrophic, 1, digenic	192600	AD	3	MYLK2	606566

Clinical Synopsis | Phenotypic Series

www.omim.org.

#192600
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Genetic Heterogeneity of Hypertrophic Cardiomyopathy

Additional forms of hypertrophic cardiomyopathy include CMH2 (115195), caused by mutation in the TNNT2 gene (191045) on chromosome 1q32; CMH3 (115196), caused by mutation in the TPM1 gene (191010) on chromosome 15q22; CMH4 (115197), caused by mutation in the MYBPC3 gene (600958) on chromosome 11p11; CMH6 (600858), caused by mutation in the PRKAG2 gene (602743) on chromosome 7q36; CMH7 (613690), caused by mutation in the TNNI3 gene (191044) on chromosome 19q13; CMH8 (608751), caused by mutation in the MYL3 gene (160790) on chromosome 3p21; CMH9 (see 188840), caused by mutation in the TTN gene (188840) on chromosome 2q31; CMH10 (see 160781), caused by mutation in the MYL2 gene (160781) on chromosome 12q24; CMH11 (612098), caused by mutation in the ACTC1 gene (102540) on chromosome 15q14; CMH12 (612124), caused by mutation in the CSRP3 gene (600824) on chromosome 11p15; CMH13 (613243), caused by mutation in the TNNC1 gene (191040) on chromosome 3p21; CMH14 (613251), caused by mutation in the MYH6 gene (160710) on chromosome 14q12; CMH15 (613255), caused by mutation in the VCL gene (193065) on chromosome 10q22; CMH16 (613838), caused by mutation in the MYOZ2 gene (605602) on chromosome 4q26; CMH17 (613873), caused by mutation in the JPH2 gene (605267) on chromosome 20q12; CMH18 (613874), caused by mutation in the PLN gene (172405) on chromosome 6q22; CMH19 (613875), caused by mutation in the CALR3 gene (611414) on chromosome 19p13; CMH20 (613876), caused by mutation in the NEXN gene (613121) on chromosome 1p31.1; CMH21, mapped to chromosome 7p12.1-q21; CMH22 (see 615248), caused by mutation in the MYPN gene (608517) on chromosome 10q21; CMH23 (see 612158), caused by mutation in the ACTN2 gene (102573) on chromosome 1q43; CMH24 (see 601493), caused by mutation in the LDB3 gene (605906) on chromosome 10q23; CMH25 (607487), caused by mutation in the TCAP gene (604488) on chromosome 17q12; and CMH26 (617047), caused by mutation in the FLNC gene (102565) on

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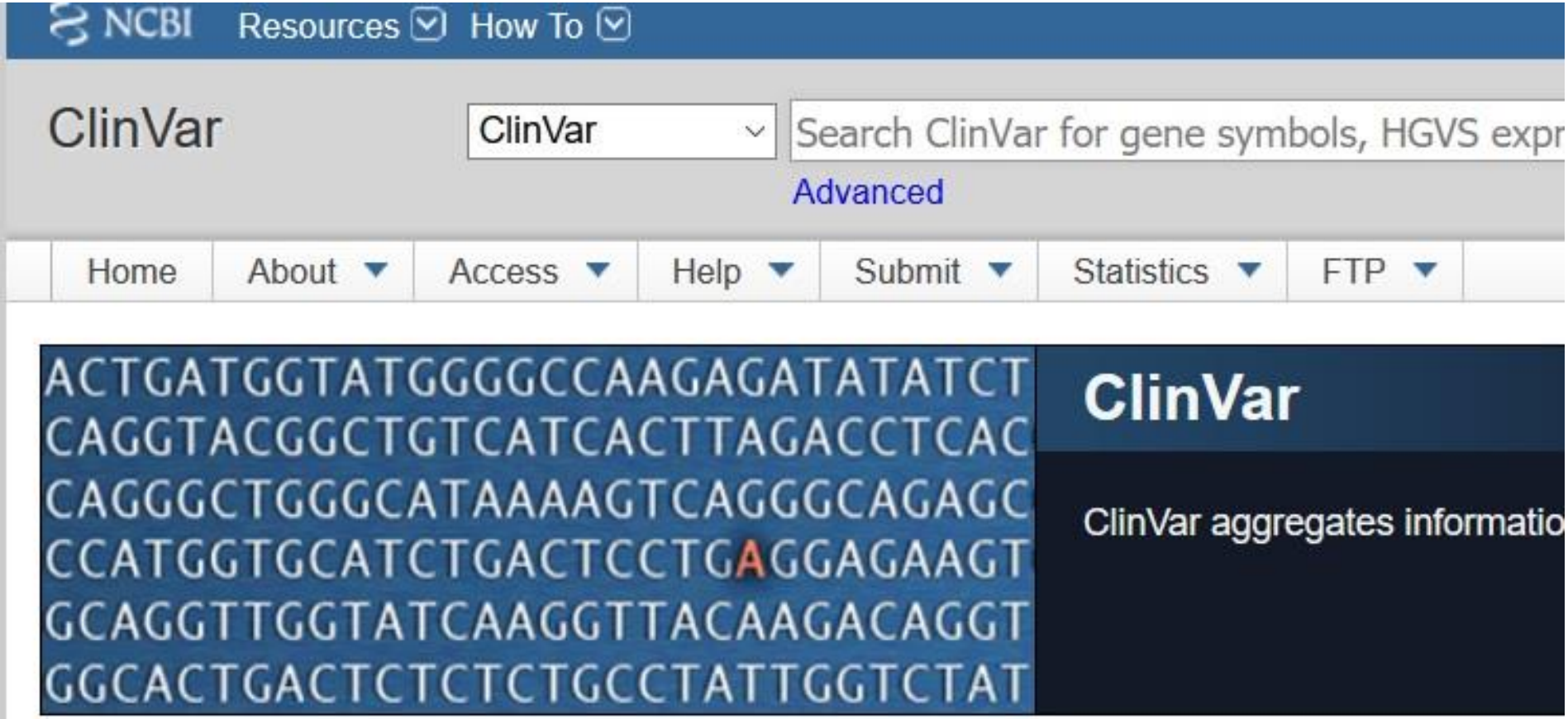


„…freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence…“

https://www.ncbi.nlm.nih.gov/clinvar/

Published in final edited form as:
Genet Med. 2015 May ; 17(5): 405–424. doi:10.1038/gim.2015.30.

Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards [Chair, ACMG],
Knight Diagnostic Laboratories; Department of Molecular and Medical Genetics; Oregon Health & Science University, Portland, OR, USA

Klasifikace mutací - 5 tříd:

5) patogenní
4) pravděpodobně patogenní
3) nejasného významu - VUS
2) pravděpodobně benigní
1) benigní

Richards S et al., Genet Med. 2015

Principy klasifikace variant

- Frekvence variant v kontrolní populaci, s využitím mezinárodních databází (např. 1000Genomes Project, Exome Sequencing Project, Exome Aggregation Consortium)
- Publikované varianty asociované s onemocněním (např. Clinvar, Human Gene Mutation Database)
- *In silico* klasifikace s užitím softwaru (např. Polyphen2, Sorting Intolerant From Tolerant) predikujícím možný dopad mutace na strukturu a funkci výsledného proteinu
- Mutace v tzv. evolučně vysoce konzervovaných funkčních doménách proteinů
- Segregační analýzy genotypu s fenotypem v postižených rodinách (silná evidence)
- Funkční studie na animálních modelech či *in vitro* (nákladné, složité)

Mayo Score

+ 1

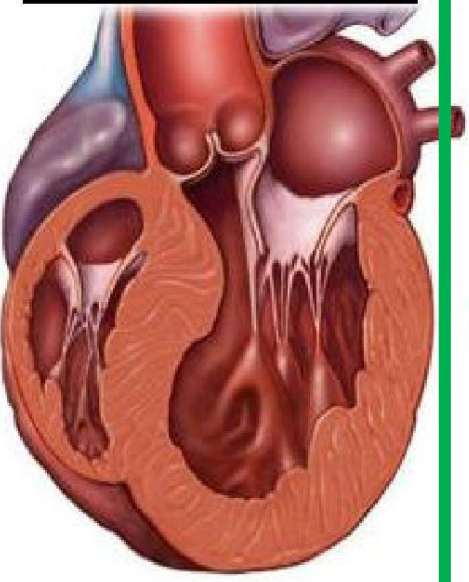
- Věk < 45 let
- Tloušťka stěny levé komory ≥ 20 mm
- Rodinná anamnéza HCM
- Rodinná anamnéza náhlé srdeční smrti
- Reversní (katenoidní) tvar septa

- Arteriální hypertenze

- 1

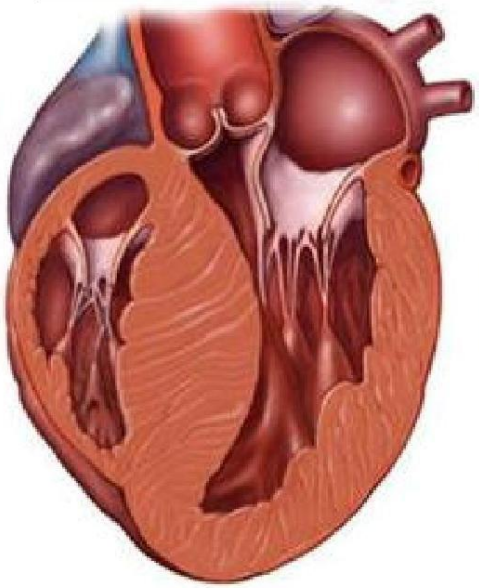
Bos JM, et al. 2014

Sigmoidal HCM
40 - 50%



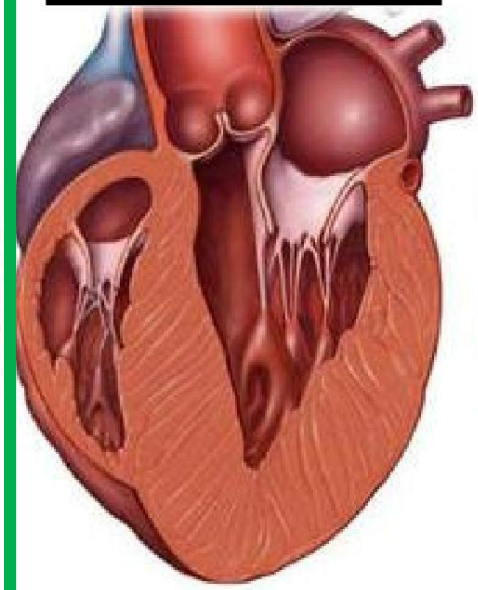
~ 10% Myofilament Gene +

Reverse curve HCM
30 - 40%



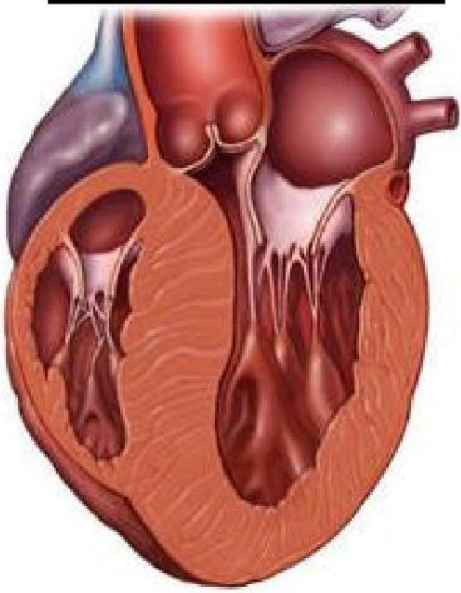
~ 80% Myofilament Gene +

Apical HCM
~ 10%



~ 30% Myofilament Gene +

Neutral HCM
~ 10%



~ 40% Myofilament Gene +

Bos JM, et al. 2009

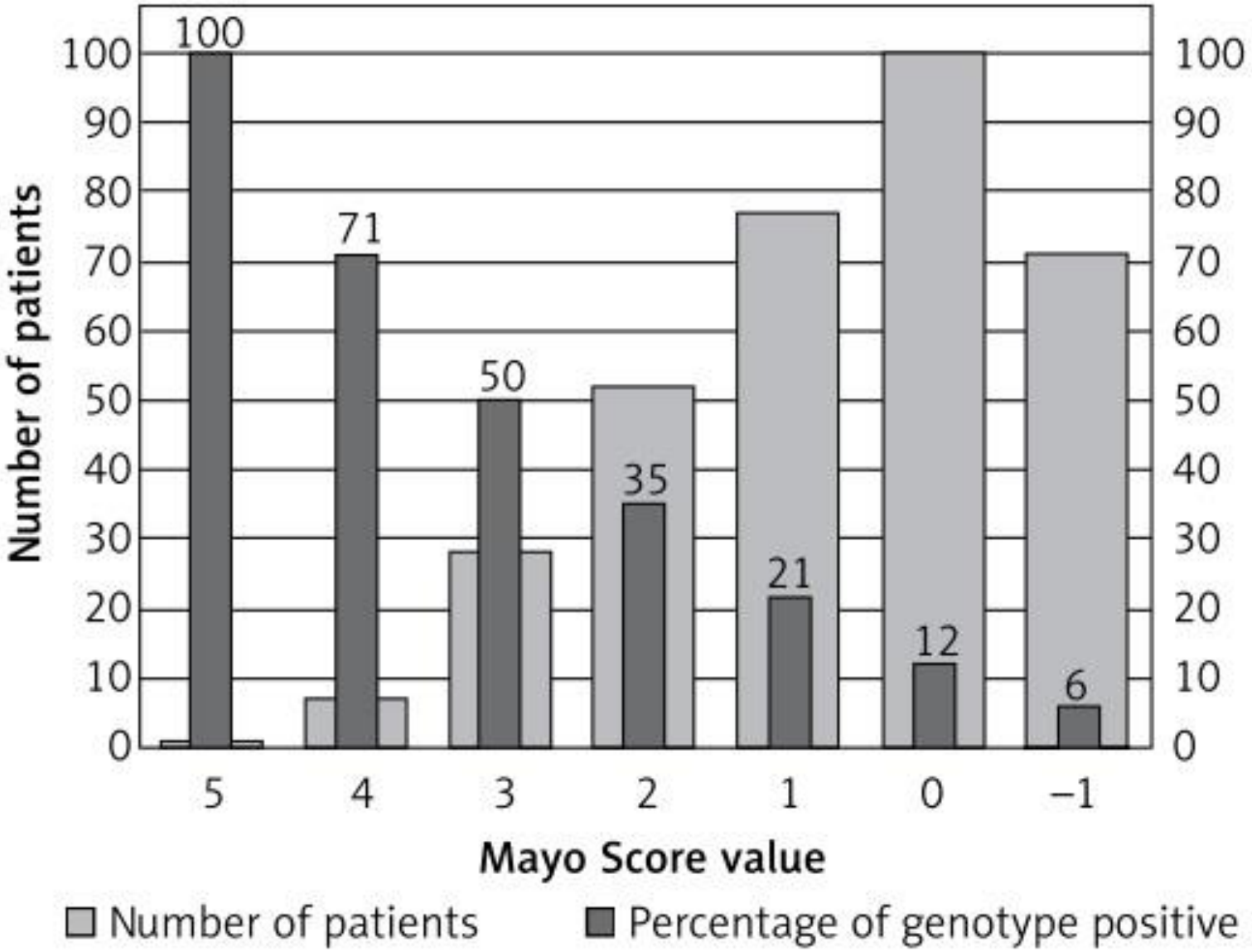


Figure 2. Mayo Score and positive genotype in HCM patients

Bonaventura J, et al. 2018

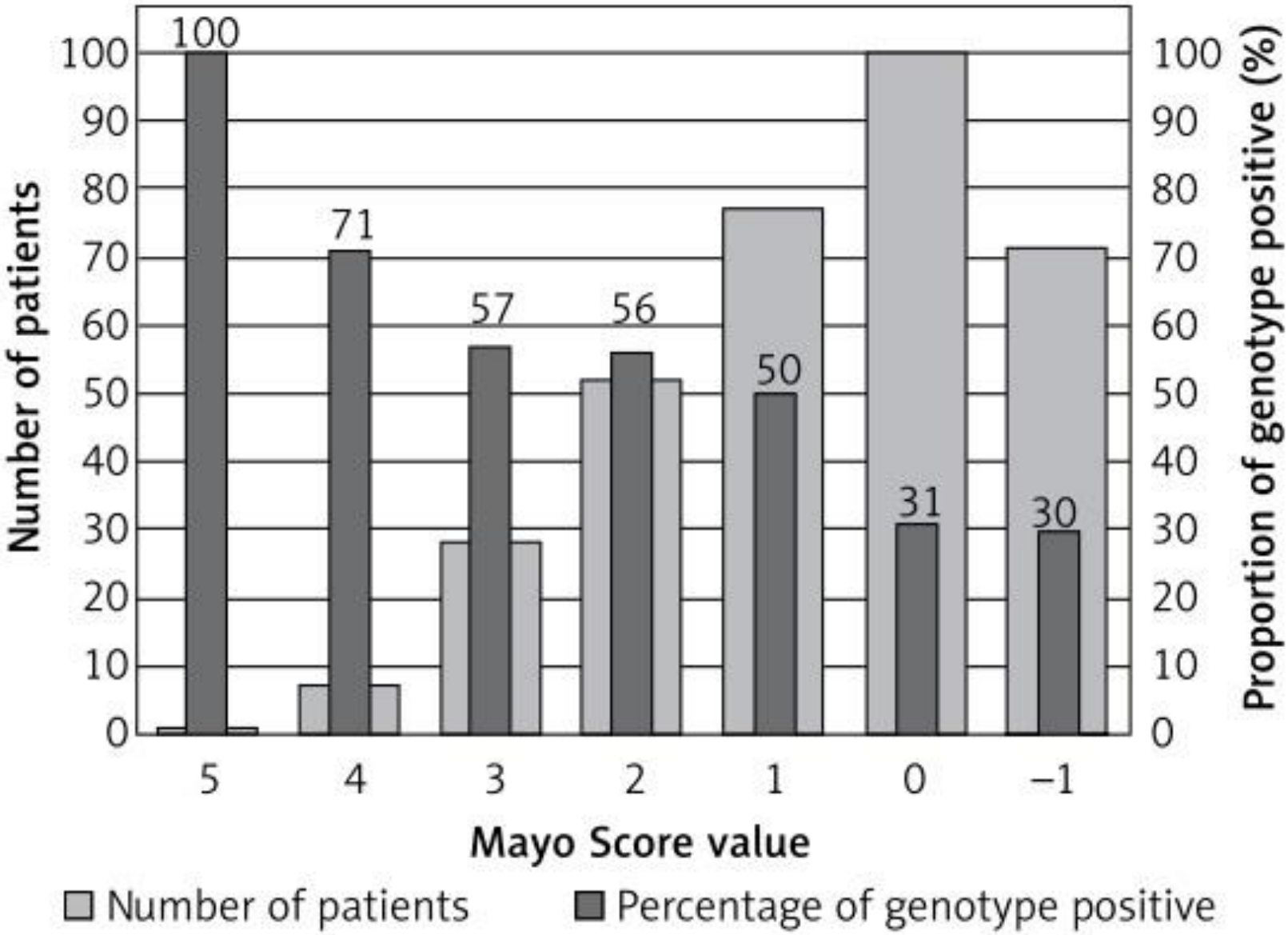


Figure 3. Mayo Score in HCM patients when VUS are considered positive genotype

Bonaventura J, et al. 2018

Prognostický význam?

Circulation

ORIGINAL RESEARCH ARTICLE

Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy

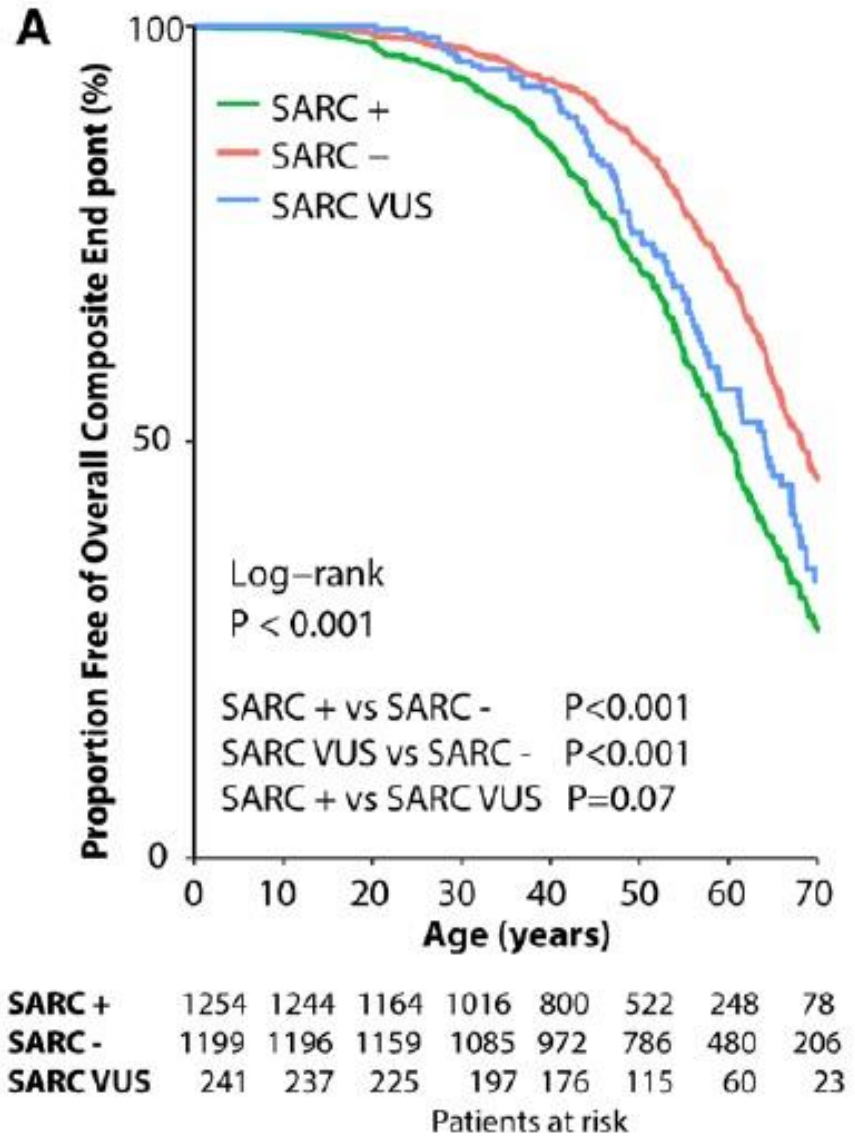
Insights From the Sarcomeric Human Cardiomyopathy Registry (SHaRe)

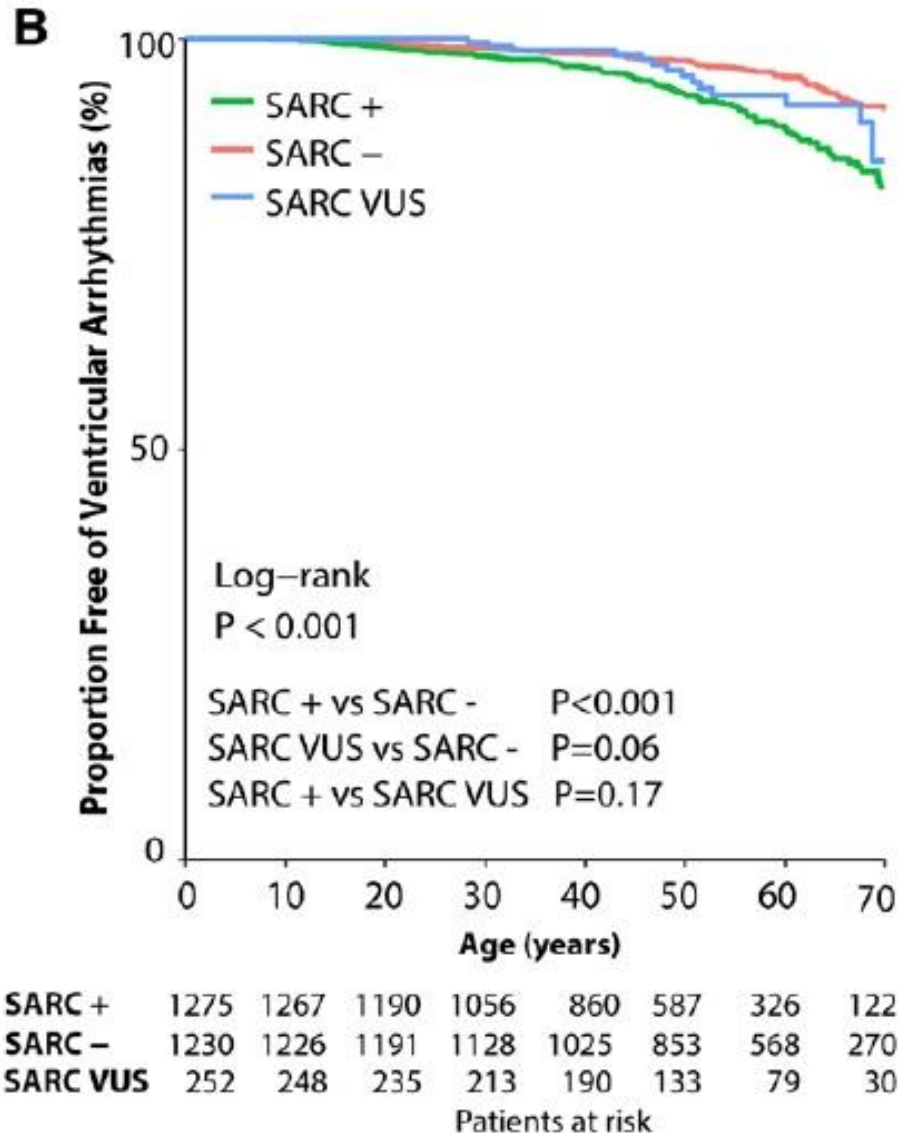
4591 patients with HCM (2763 genotyped), mean of 5.4 ± 6.9 years FU

Patients with **pathogenic/likely pathogenic sarcomere mutations**
had a **2-fold greater risk** for AE compared with patients without mutations

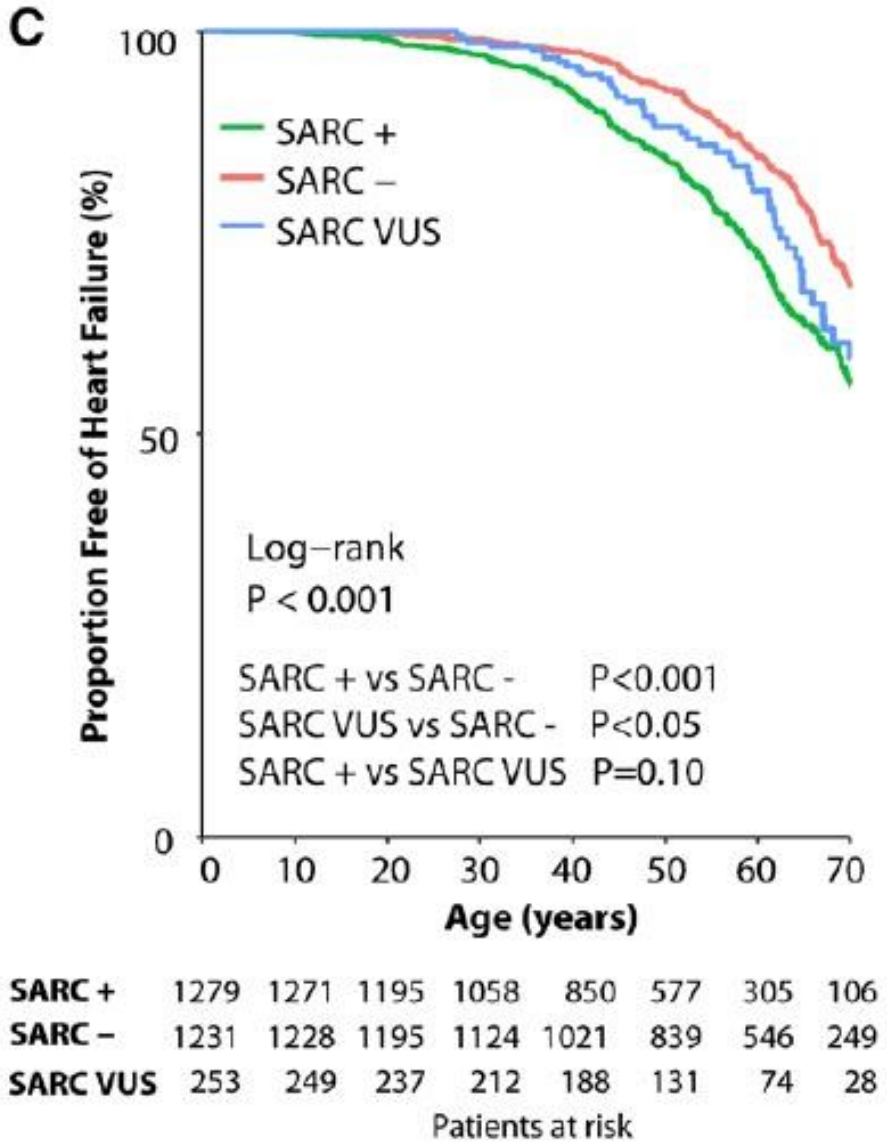
sarcomere variants of uncertain significance were associated with intermediate risk

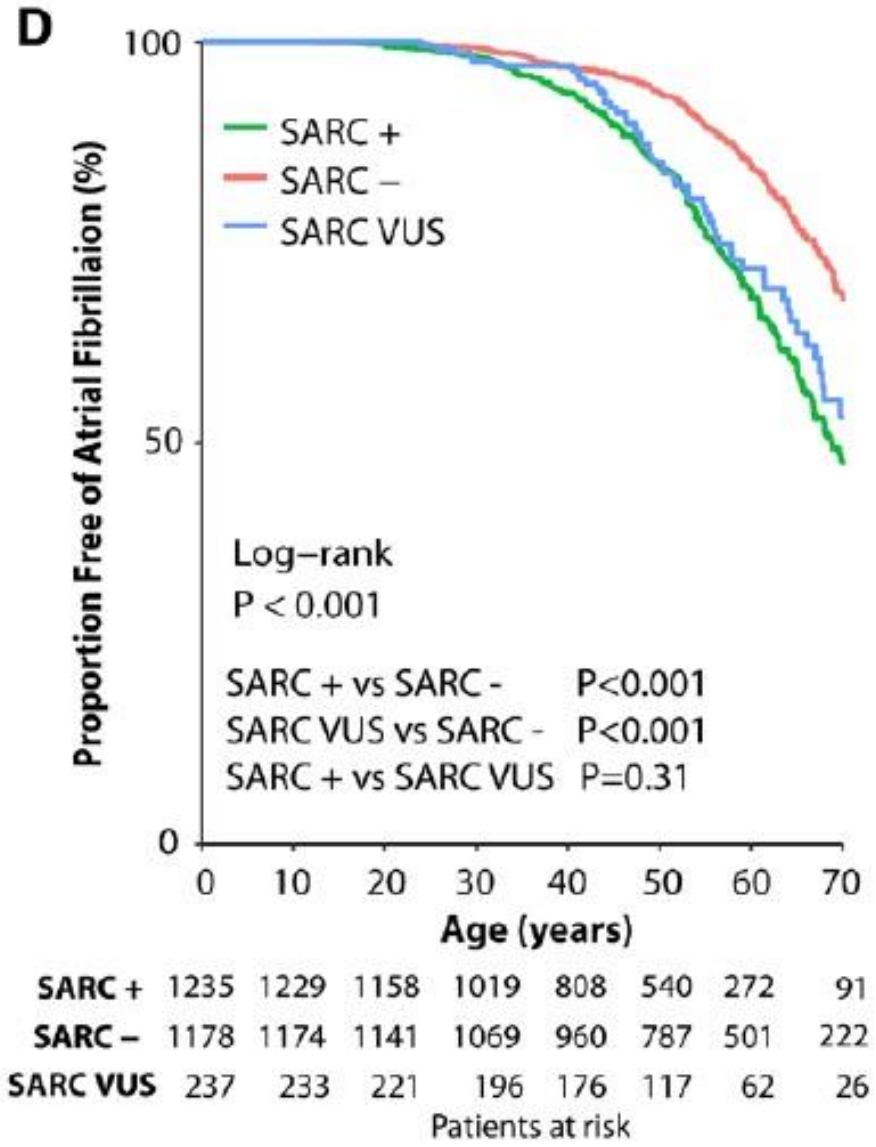
Ho CY, et al., 2018





Ho CY, et al., 2018





Ho CY, et al., 2018

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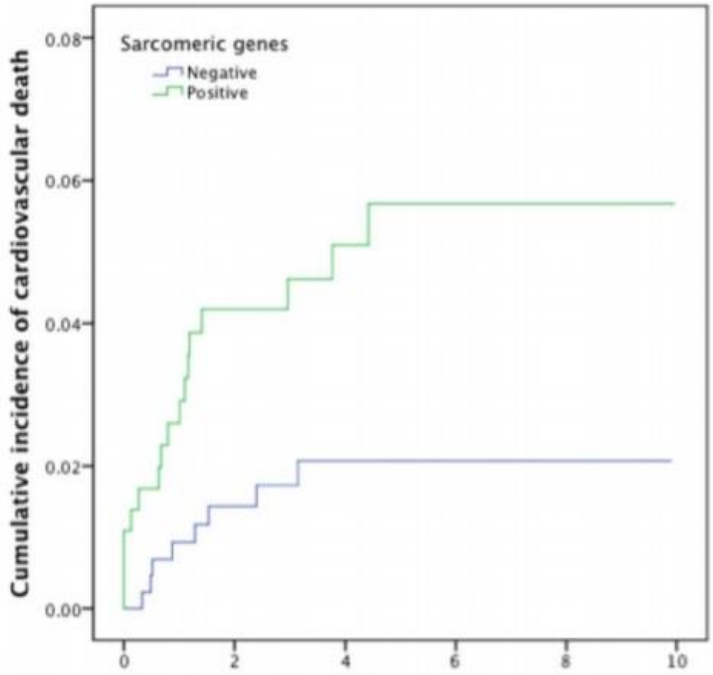
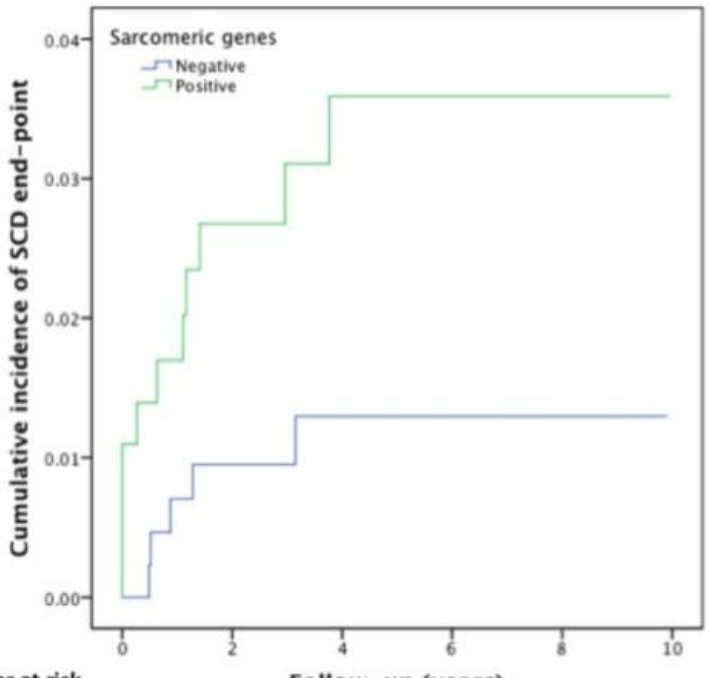


Number at risk						
Sarcomeric gene -positive	383	292	204	129	62	17
Sarcomeric gene -negative	491	382	259	159	81	20

A



Number at risk						
Sarcomeric gene -positive	383	292	204	129	62	17
Sarcomeric gene -negative	491	382	259	159	81	20

Lopes LR et al., 2015

Genetic Evaluation of Cardiomyopathy
A Heart Failure Society of America
Practice Guideline

Hershberger, et al. 2018

Cardiomyopathy	Core Genes*	Estimates of Genetic Testing Diagnostic Yield
HCM	*MYH7*, *MYBPC3*, *TNNT2*, *TNNC1*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, *ACTN2*, *CSRP3*, *PLN*, *TTR*, *PRKAG2*, *LAMP2*, *GLA*	30%–60%
DCM	*TTN*,† *LMNA*, *MYH7*, *TNNT2*, *BAG3*, *RBM20*, *TNNC1*, *TNNI3*, *TPM1*, *SCN5A*, *PLN*. For testing, all HCM and	10%–40%

Souhrn

- Některé HCM jsou pravděpodobně monogenně podmíněná onemocnění (AD)
- Neúplná penetrance, variabilní expresivita
- 26 + genů i mutací (MYBPC3, MYH7)
- Sarkomerické mutace – prognostické?
- Proband, kaskádové testování
- Výtěžnost gen. vyšetření variabilní (20-40%?), lze predikovat (Mayo score)
- Genetické poradenství, klasifikace variant

Děkuji za pozornost.