FN MOTOL

KARDIOLOGICKÁ KLINIKA
2. LF UK a FN MOTOL

Kardiomyopatie klasifikace, genetika

Jiří Bonaventura

Kardiologická klinika 2. LF UK a FN Motol

Kardio 35 „Vše, co potřebujete vědět o kardiomyopatiích před kardiologickou atestací“

FN Motol, 30.3.2019

10%

Atestace z kardiologie - otázky

5) **Kardiomyopatie**

Pravostranná srdeční katetrizace
Pozitivně inotropní látky

7) **Hypertrofická kardiomyopatie**

Perkutánní koronární intervence
Antiarytmika

8) **Dilatační kardiomyopatie**

Nekoronární perkutánní intervence
Sartany

9) **Restriktivní kardiomyopatie**

Patofyziologie žilní trombózy
Diuretika

10) **Myokarditida a zánětlivá kardiomyopatie**

Elektrofyziologické vyšetření
Fibrinolytická léčba

Historie

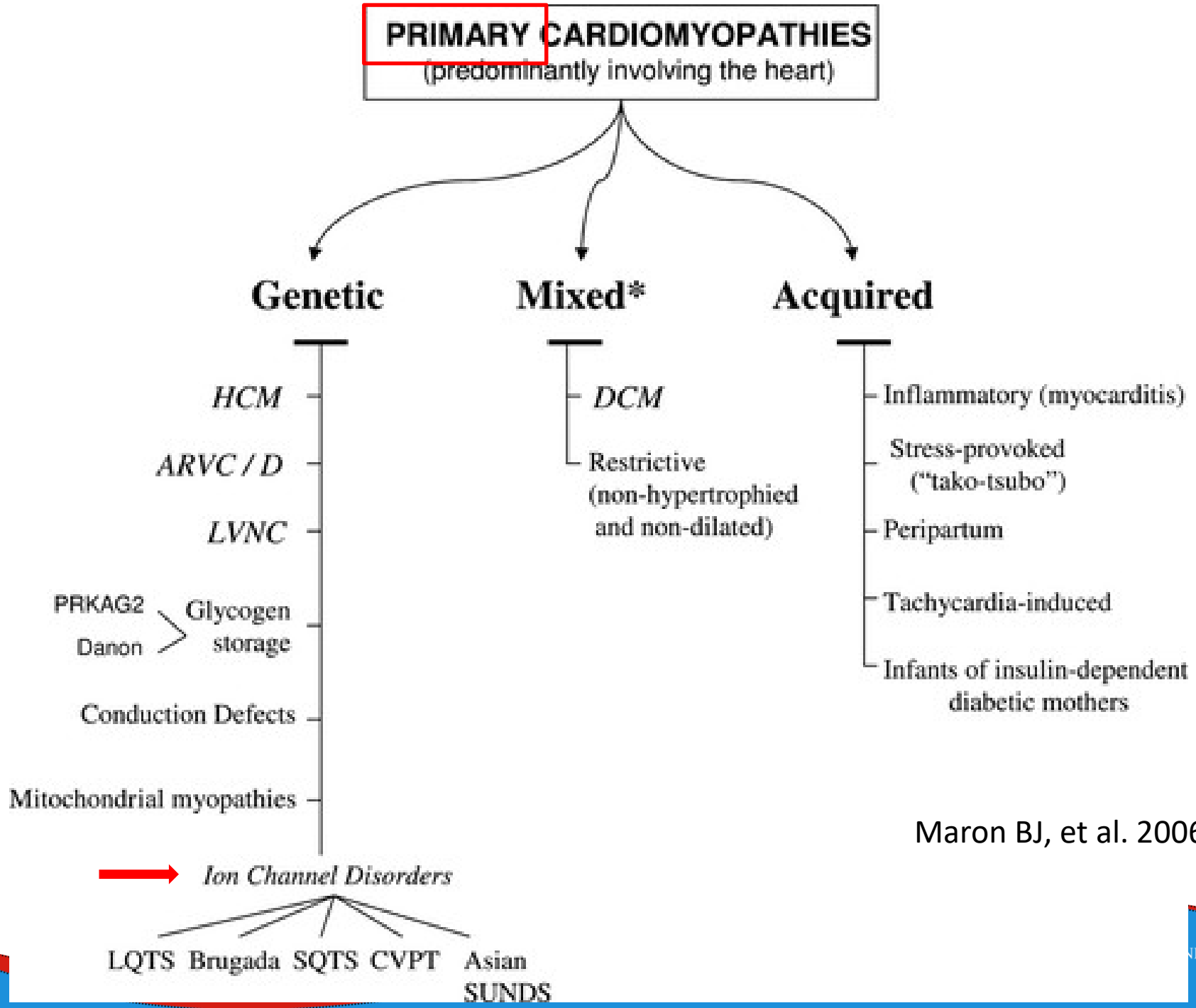
- 1957 – termín *„cardiomyopathy“*
- 1968 WHO *“diseases of different and often unknown etiology in which the dominant feature is cardiomegaly and heart failure.”*
- 1980 WHO - *“heart muscle diseases of unknown cause”* – HCM, DCM, RCM
- 1995 WHO *“diseases of myocardium associated with cardiac dysfunction”* – primární (HCM, DCM, RCM, ARVC) x specifické
- **2006 – AHA a ESC klasifikace**

Richardson P, et al. 1996
Abelmann WH, et al. 1984

AHA 2006 definice

- *„Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability.“*

Maron BJ, et al. 2006



Maron BJ, et al. 2006

Sekundární kardiomyopatie I (AHA 2006)

Infiltrative

- Amyloidosis (primary, familial, senile, secondary forms)
- Gaucher disease
- Hurler's disease
- Hunter's disease

Storage

- Hemochromatosis
- Fabry's disease
- Glycogen storage disease (type II, Pompe)
- Niemann-Pick disease

Toxicity

- Drugs, heavy metals, chemical agents

Endomyocardial

- Endomyocardial fibrosis
- Hypereosinophilic syndrome (Löeffler's endocarditis)

Maron BJ, et al. 2006

Sekundární kardiomyopatie II (AHA 2006)

Inflammatory (granulomatous)
- Sarcoidosis

Endocrine
- Diabetes mellitus
- Hyperthyroidism
- Hypothyroidism
- Hyperparathyroidism
- Pheochromocytoma
- Acromegaly

Cardiofacial
- Noonan syndrome
- Lentiginosis

Neuromuscular/neurological
- Friedreich's ataxia
- Duchenne-Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- Myotonic dystrophy
- Neurofibromatosis
- Tuberous sclerosis

Maron BJ, et al. 2006

Sekundární kardiomyopatie III (AHA 2006)

Nutritional deficiencies

Beriberi, pallagra, scurvy, selenium, carnitine, kwashiorkor

Autoimmune/collagen

Systemic lupus erythematosis
Dermatomyositis
Rheumatoid arthritis
Scleroderma
Polyarteritis nodosa

Electrolyte imbalance

Consequence of cancer therapy

Anthracyclines: doxorubicin (adriamycin), daunorubicin
Cyclophosphamide
Radiation

Maron BJ, et al. 2006

Klasifikace kardiomyopatií podle AHA 2006

Primární kardiomyopatie

geneticky podmíněné

- HKMP
- ARVC
- LVNC
- střádání glykogenu (Danonova choroba, PRKAG2)
- převodní poruchy
- mitochondriopatie
- „kanálopatie“ (syndrom Brugadových, syndrom dlouhého QT aj.)

smíšené etiologie

- DKMP
- RKMP

získané

- zánětlivá
- Tako-tsubo
- peripartální
- tachykardií indukovaná
- u dětí matek trpících T1DM

Sekundární kardiomyopatie

- infiltrativní
- u střádavých chorob
- toxické
- endomyokardiální
- granulomatózně zánětlivé
- u endokrinopatií
- kardiofaciální
- u neuromuskulárních /neurologických chorob
- při nutričních deficitech
- u kolagenóz
- v důsledku elektrolytová dysbalance
- v důsledku onkologické léčby

www.ecardio.cz

ESC 2006 definice

- *„A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality“*

Elliot P, et al. 2006

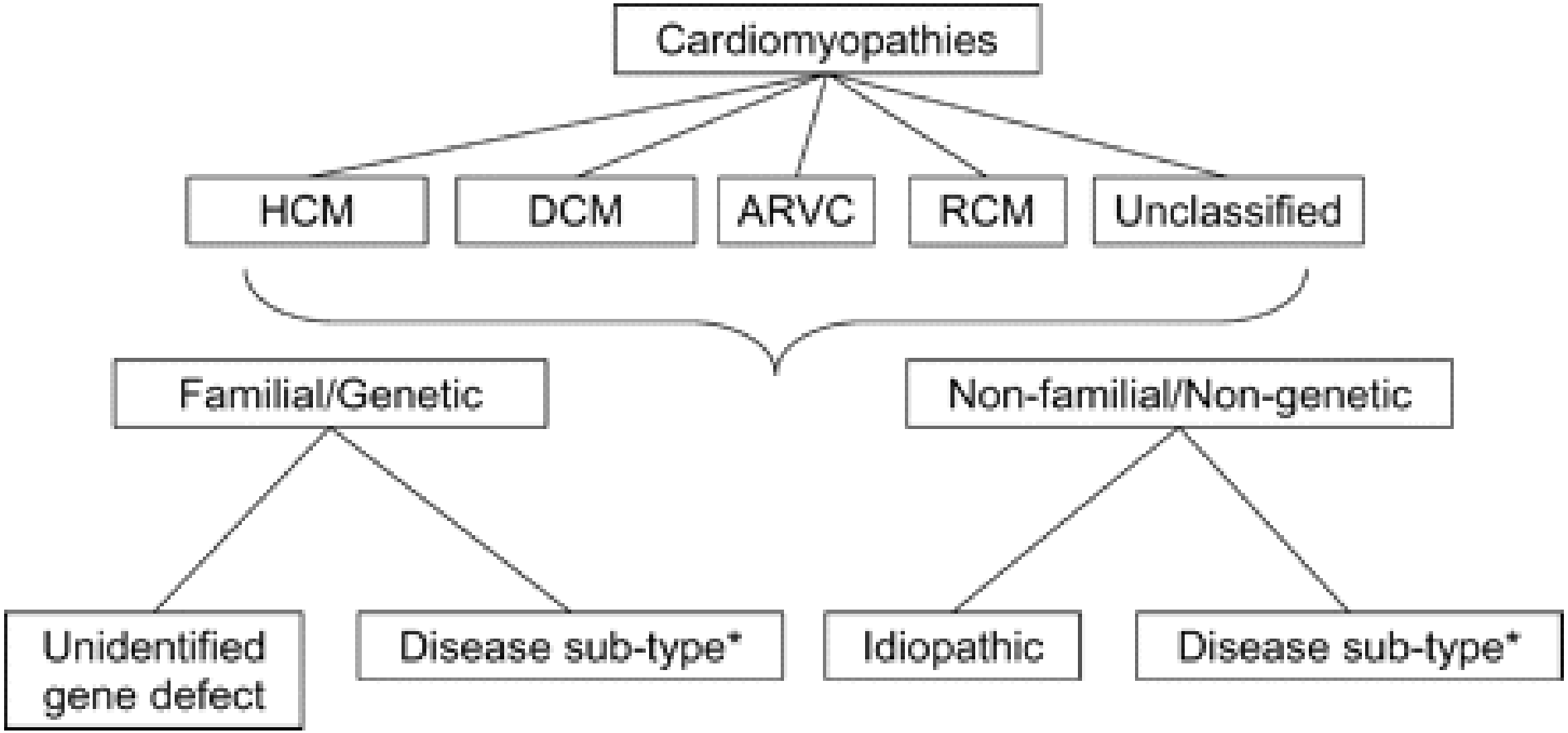
Fenotypy kardiomyopatií (ESC 2006)

- Hypertrofická kardiomyopatie (HCM)
- Dilatační kardiomyopatie (DCM)
- Restriktivní kardiomyopatie (RCM)
- Arytmogenní kardiomyopatie pravé komory (ARVC)
- Neklasifikované typy :

  Non-kompaktní kardiomyopatie (LVNC)

  Tako-tsubo kardiomyopatie

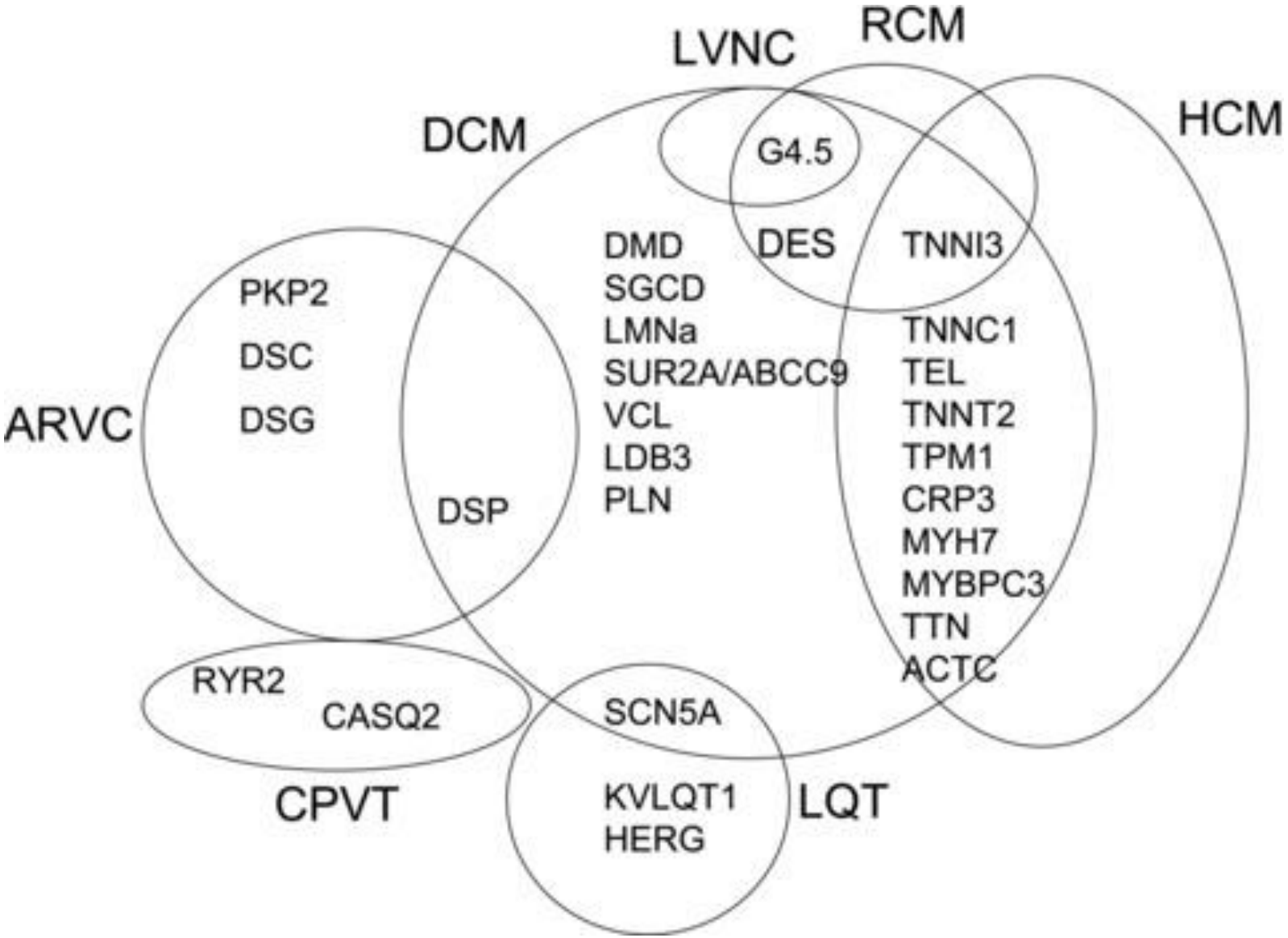
Elliot P, et al. 2006



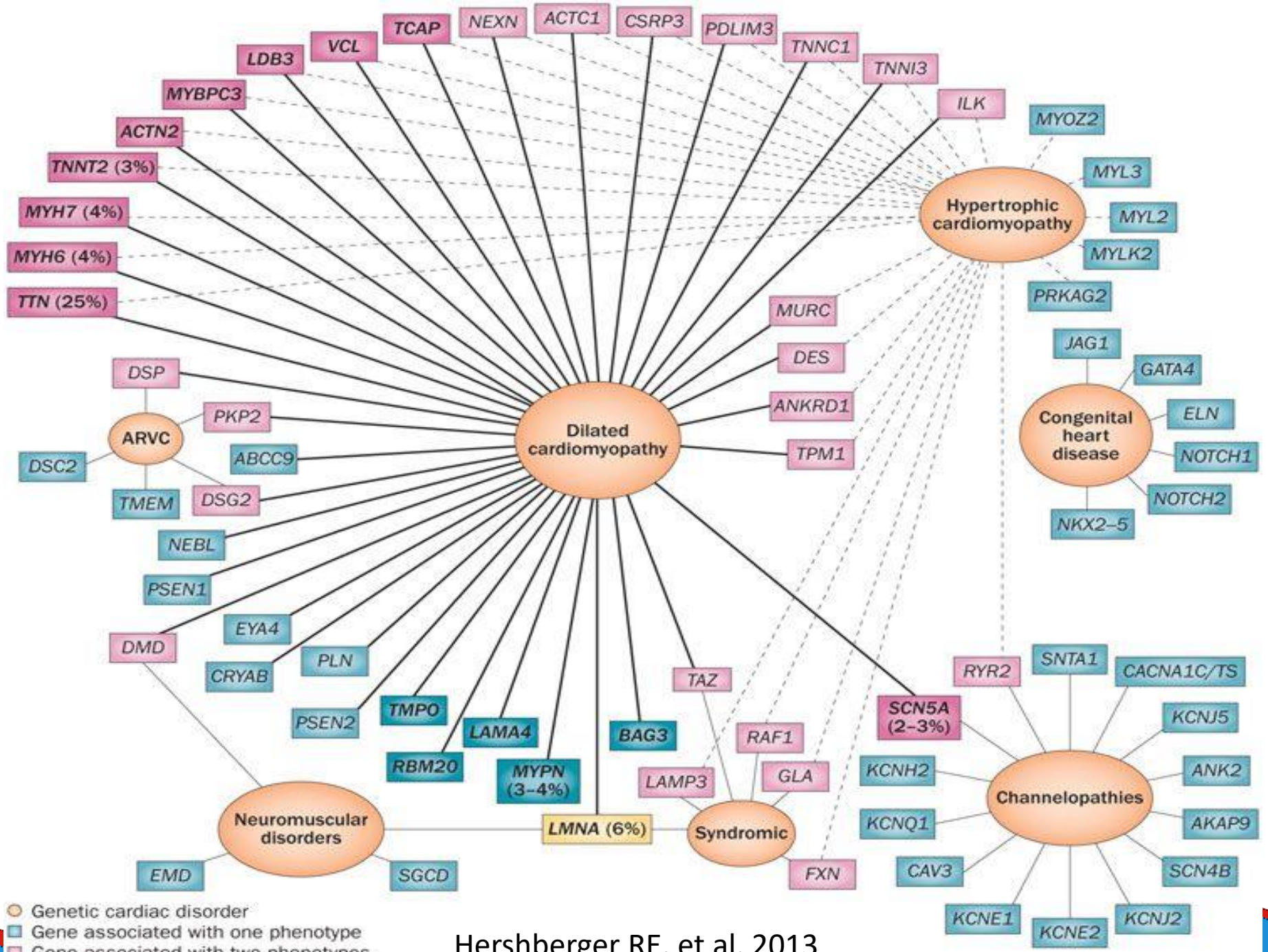
Elliot P, et al. 2006

Genetika kardiomyopatií

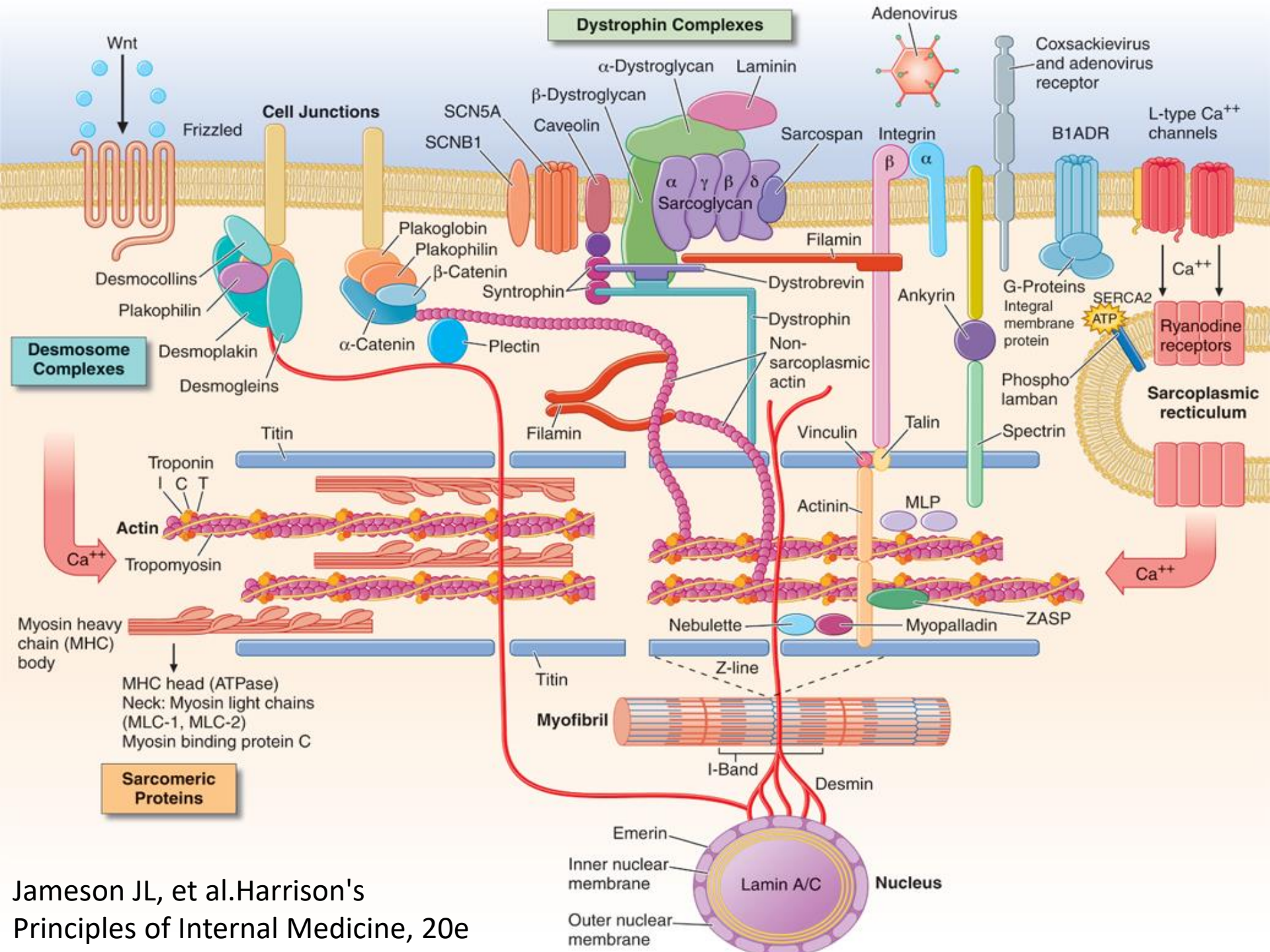
- Některé kardiomyopatie jsou monogenně podmíněná onemocnění
- Dedičnost může být AD, AR, X-vázaná i mitochondriální
- Velká genotypová variabilita - desítky genů, tisíce mutací
- Mutace v genech pro proteiny kardiomyocytů (sarkolemma, iontové kanály, kotvící proteiny, myofibrily, jaderný obal, mitochondrie,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



Maron BJ, et al. 2015



Hershberger RE, et al. 2013



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

Genetické vyšetření

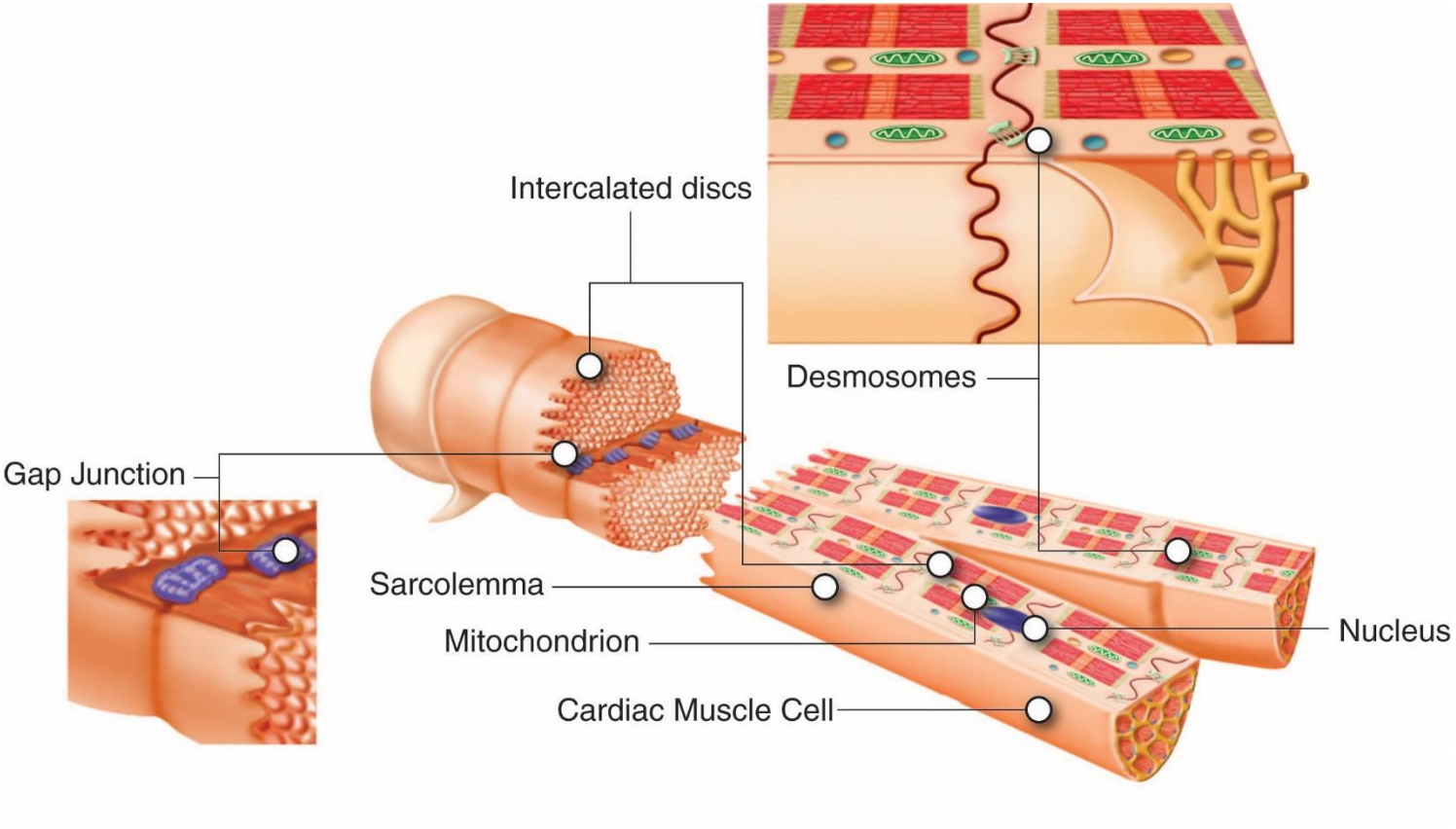
- Finančně i časově náročné (počet genů, mutací), rozvoj NGS
- Negativní výsledek **ne**znamená s jistotou nepřítomnost onemocnění
- Otazná korelace genotypu a fenotypu
- Záchyt mutací se zvyšuje u pacientů se specifickými fenotypovými rysy

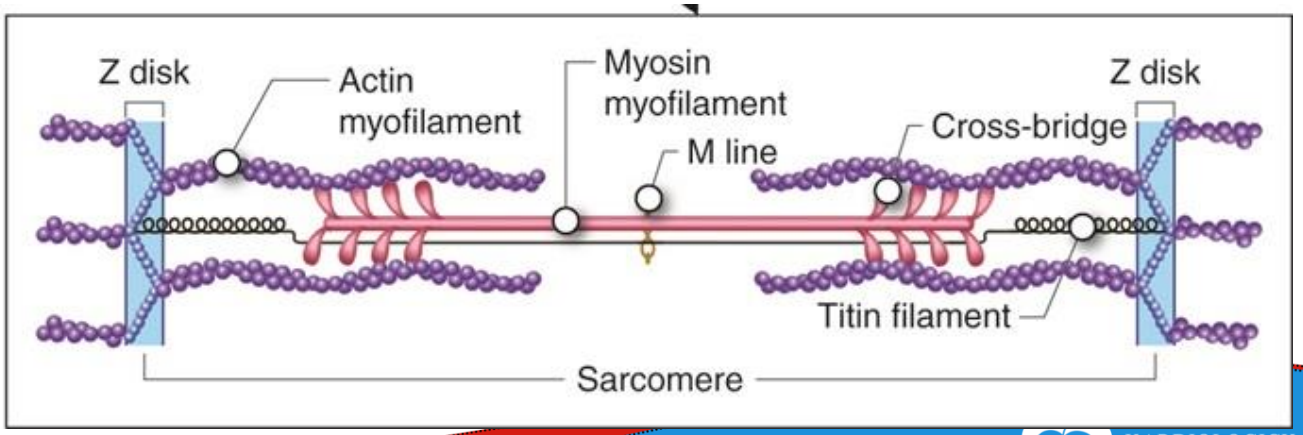
Genetika HCM

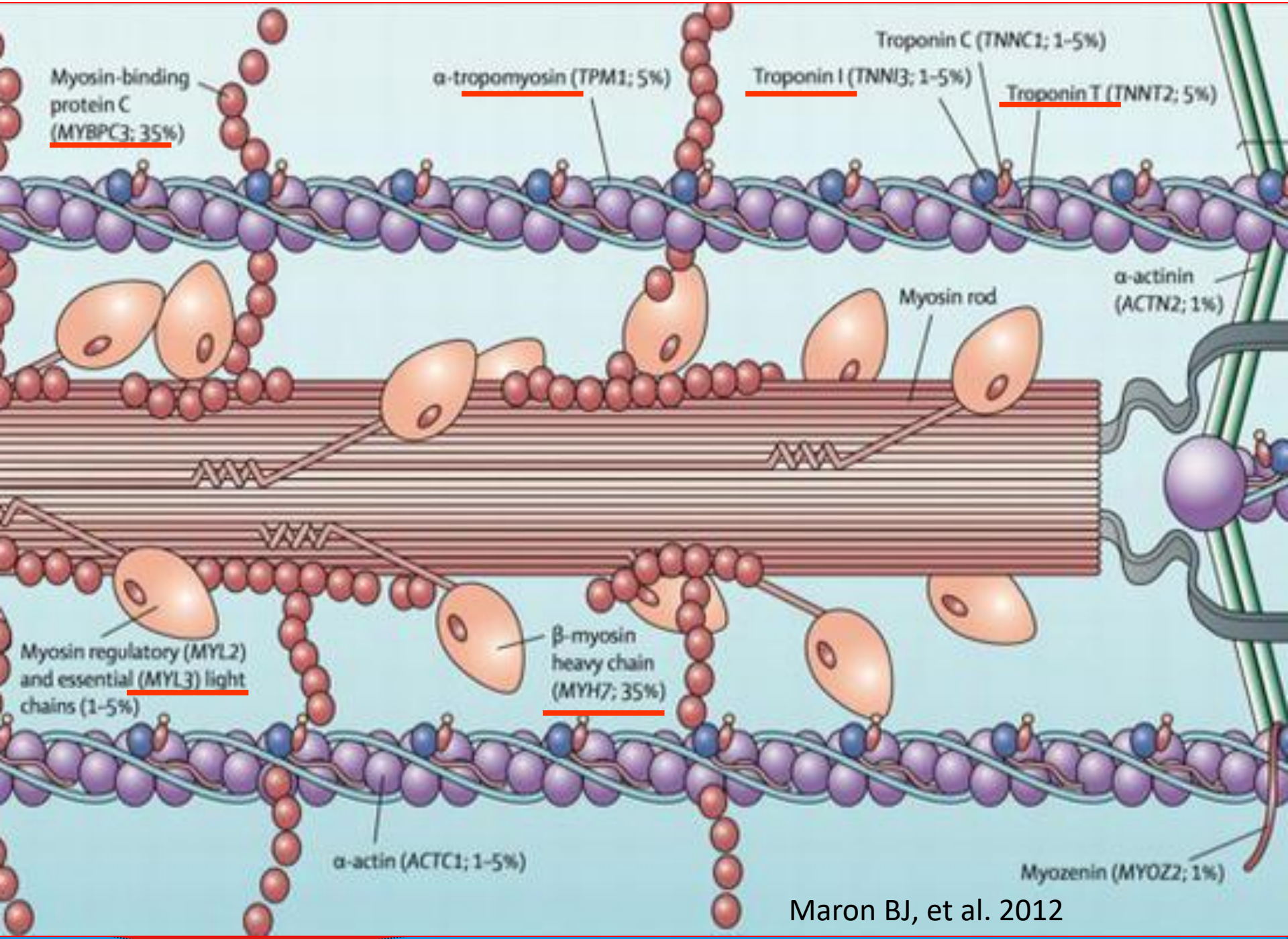
- Autosomálně dominantní dědičnost – tj. 50% riziko pro příbuzné 1. stupně?
- Mutace genů pro sarkomerické proteiny – 20-40% pacientů
- Velká genotypová i fenotypová heterogenita
  - Více než 2000 mutací v 27 genech

- ESC 2006 klasifikace : 5-10 % nemocných tvoří metabolické a neuromuskulární choroby, jiné gen. abnormality a syndromy i negenetické příčiny

www.omim.org

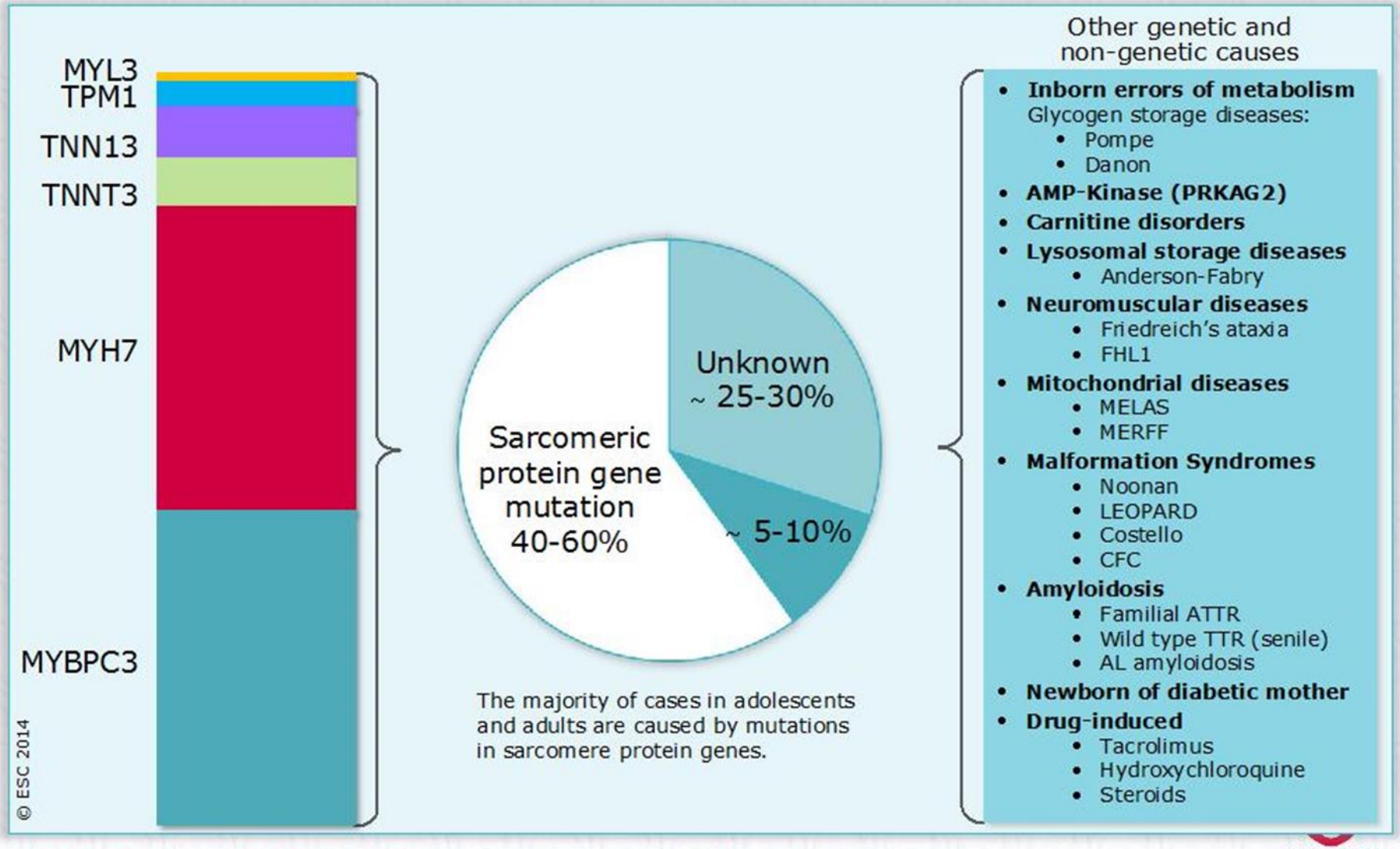

Intercalated discs
Desmosomes
Gap Junction
Sarcolemma
Mitochondrion
Nucleus
Cardiac Muscle Cell


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



Maron BJ, et al. 2012

Diverse aetiology of hypertrophic cardiomyopathy



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

EUROPEAN SOCIETY OF CARDIOLOGY®

Elliot P, et al. 2014

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

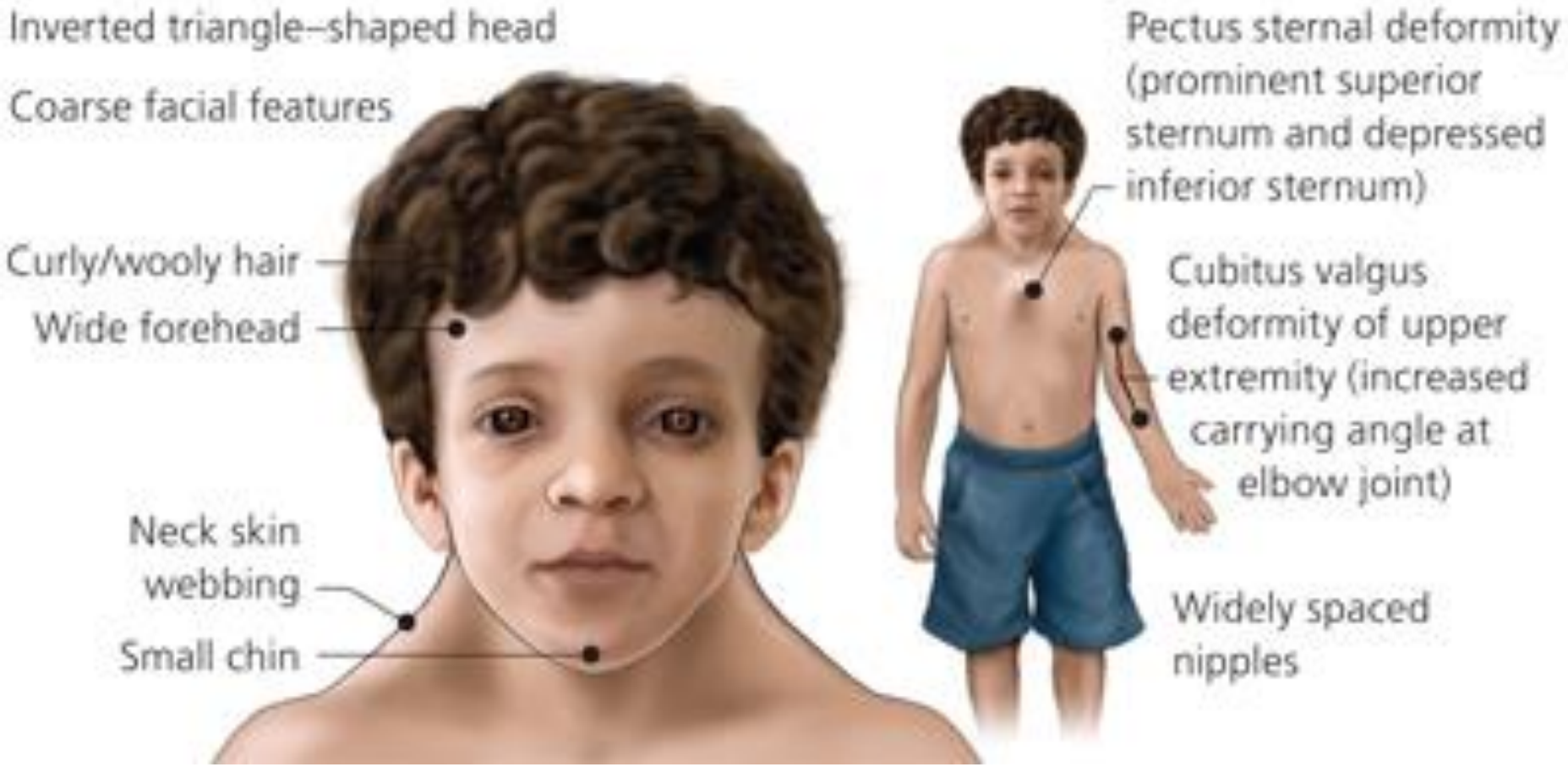
Examples of signs and symptoms suggestive of specific diagnoses *(Cont.)*

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



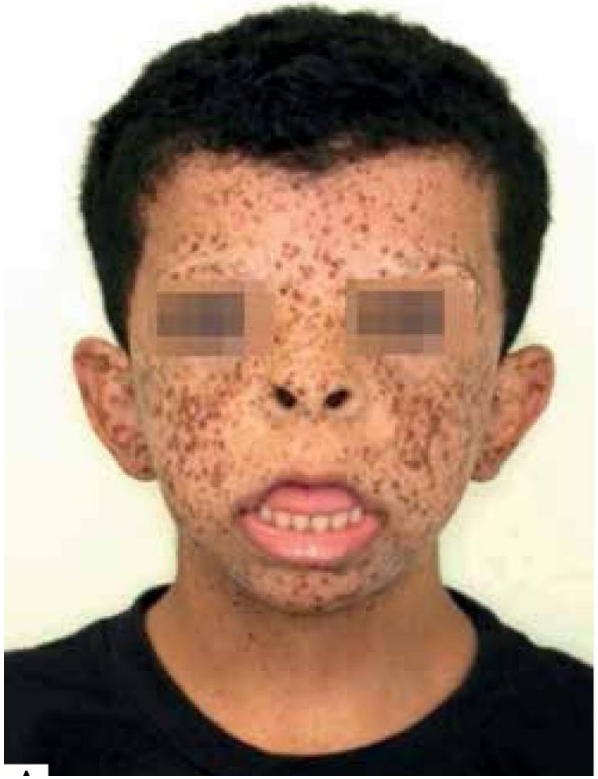
1:1000 – 1:2500

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.

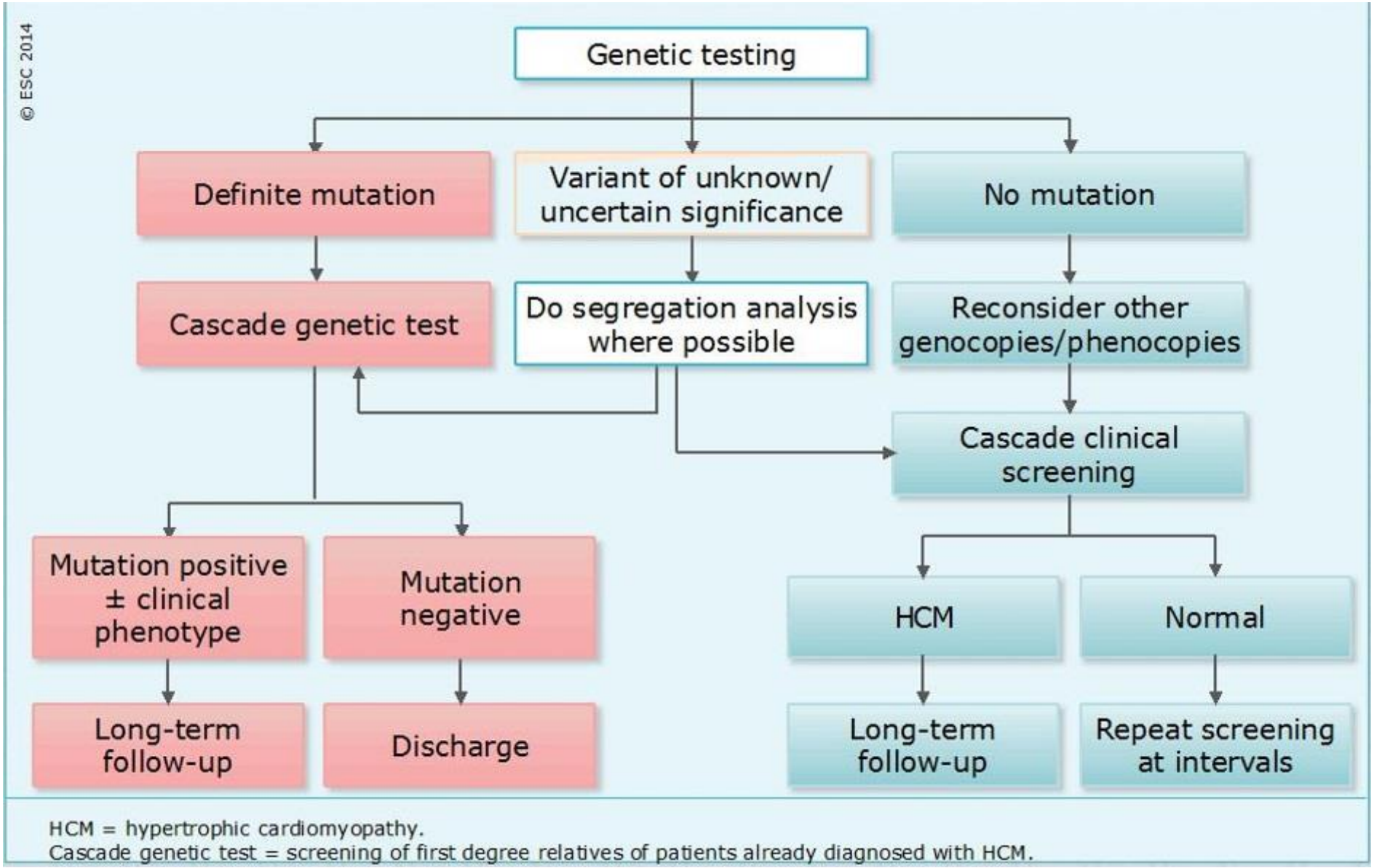
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Genetic and clinical testing of adult relatives

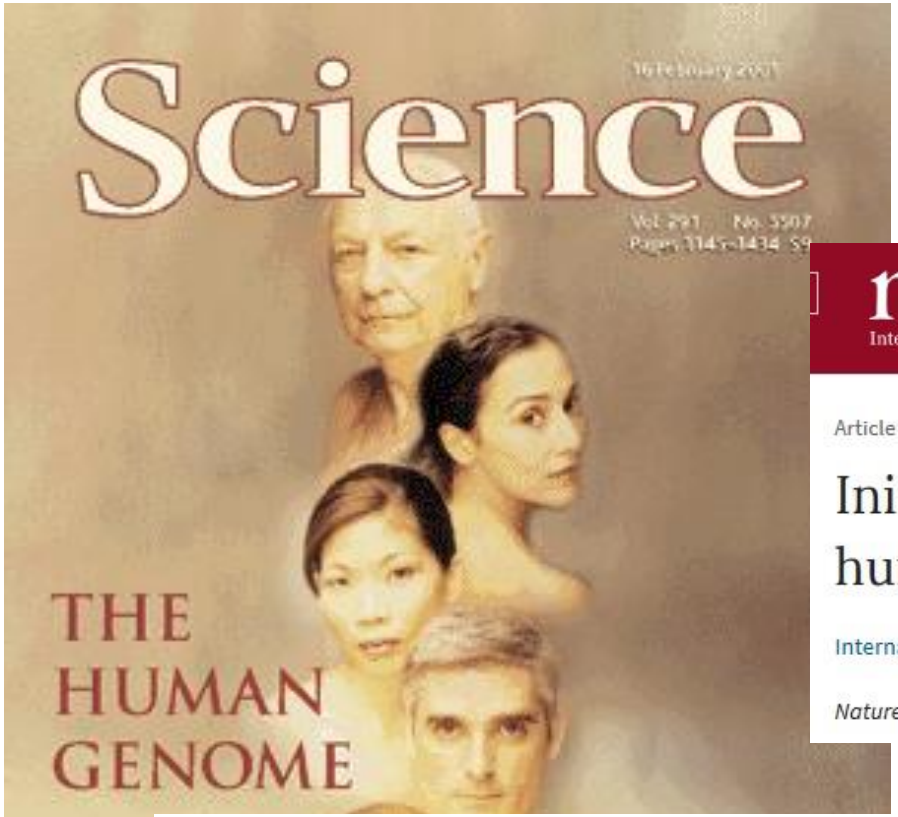
Recommendations	Class	Level
Cascade genetic screening, after pre-test counselling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation.	I	B
Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives 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

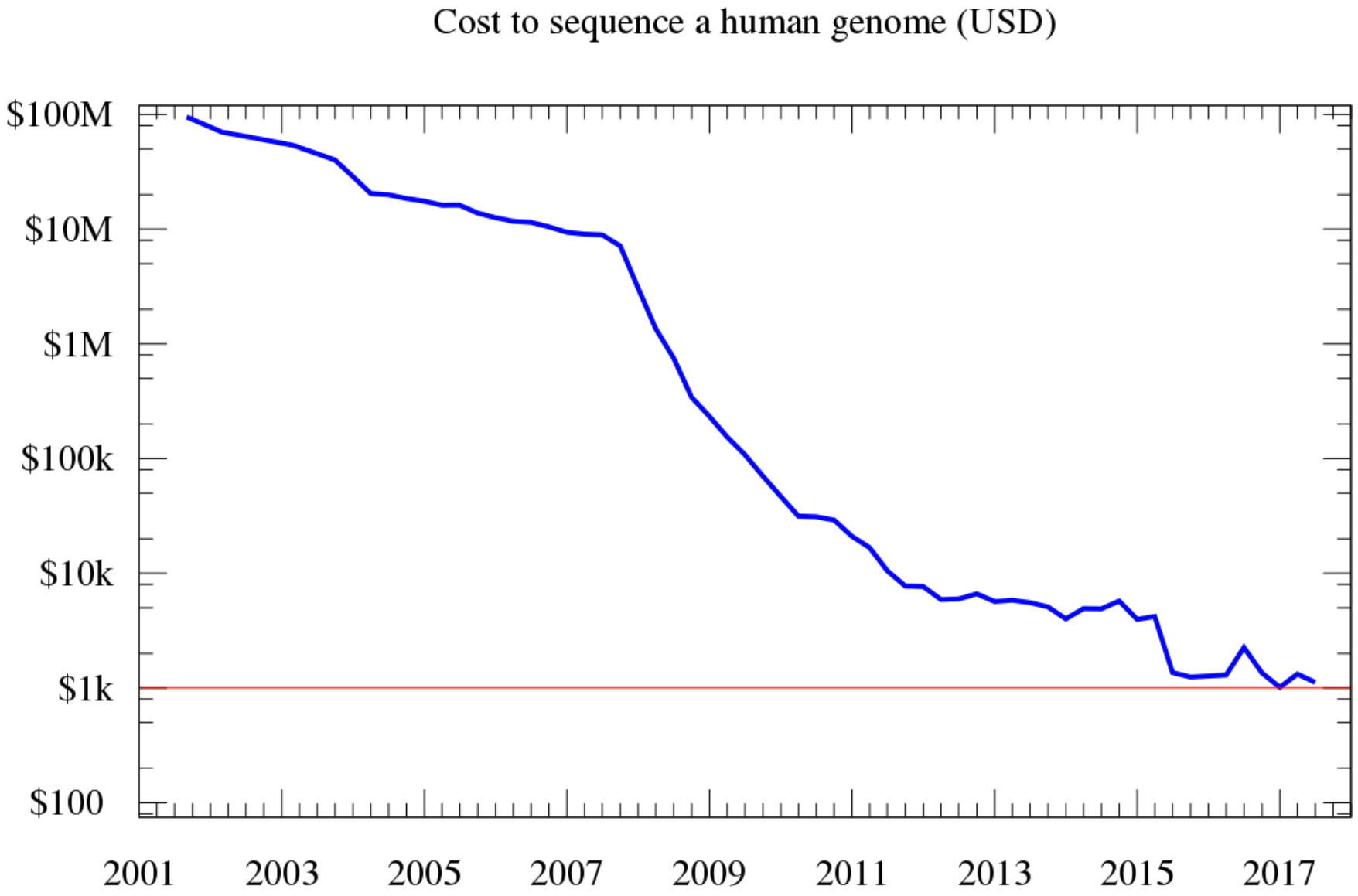
The Sequence of the Human Genome

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

- Nové metody jako NGS umožňují vyšetření velkého množství genů, ev. celého exomu
- 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 nemusí 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
Table of Contents

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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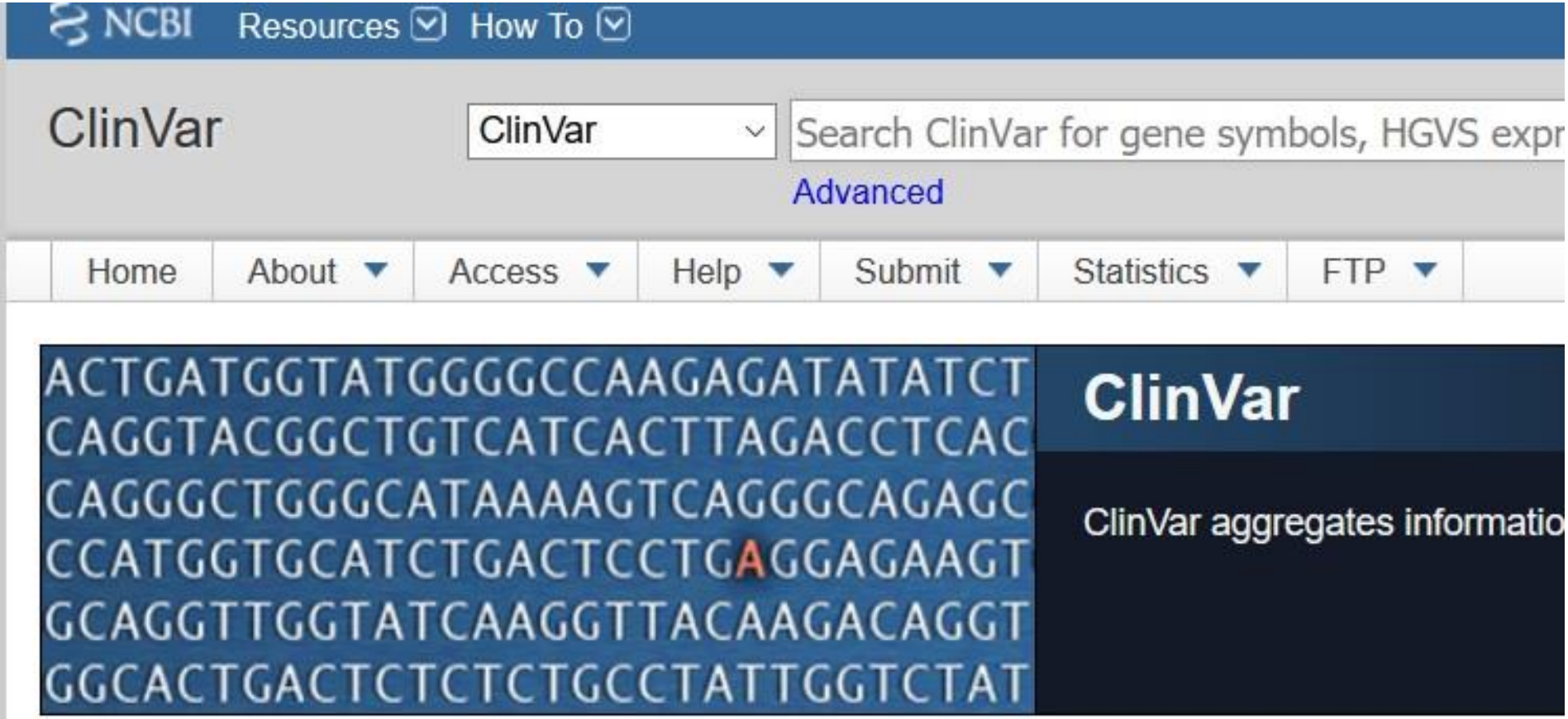


„…freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence…“

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)

Genetika HCM v klinické praxi

- AD dědičnost, sarkomerické proteiny
- Neúplná penetrance, variabilní expresivita
- 27 + genů (MYBPC3, MYH7), tisíce mutací
- Proband
- Příbuzný 1.stupně, kaskádové testování
- Klinická korelace – genotyp x fenotyp?
- Výtežnost 20-40 %, vyšší u mladších pacientů a pacientů s pozitivní rodinnou anamnézou
- Predikce výtěžnosti – Mayo Score, Toronto Score

Mayo Score

+ 1

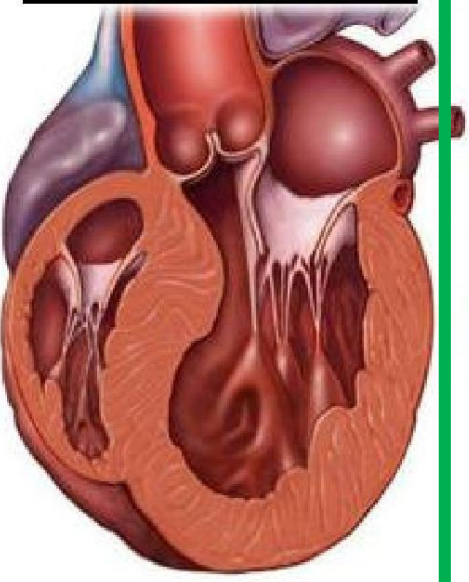
- Věk < 45 let
- Tloušťka stěny levé komory ≥ 20 mm
- Rodinná anamnéza HCM
- Rodinná anamnéza náhlé srdeční smrti
- Reversní (katenoidní) tvar septa

- Arteriální hypertenze

- 1

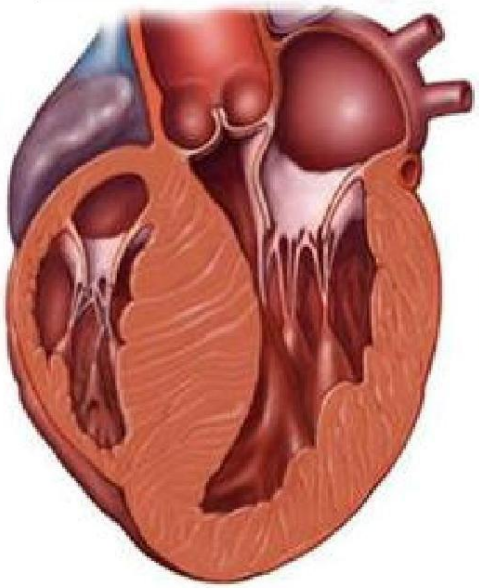
Bos JM, et al. 2014

Sigmoidal HCM
40 - 50%



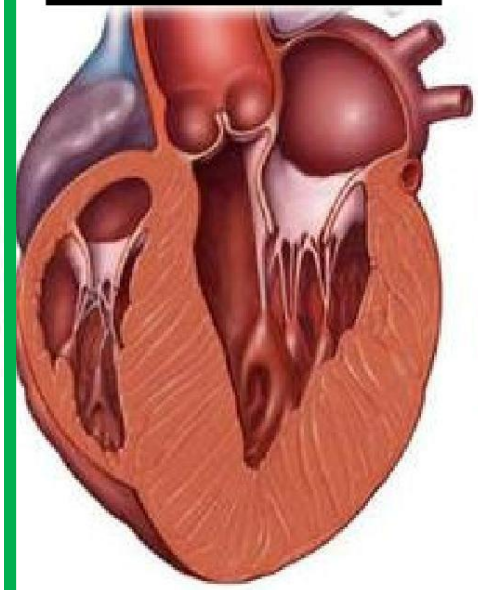
~ 10% Myofilament Gene +

Reverse curve HCM
30 - 40%



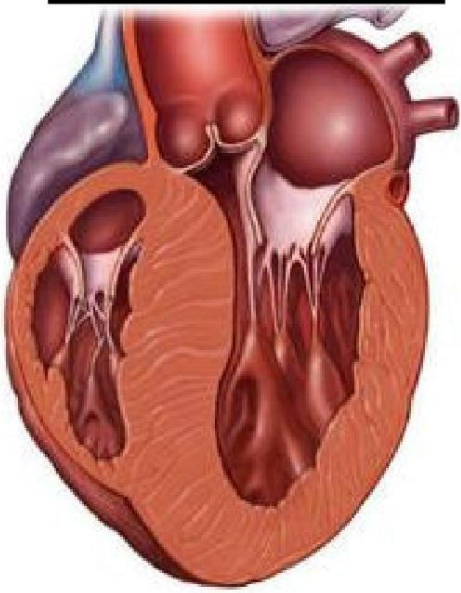
~ 80% Myofilament Gene +

Apical HCM
~ 10%



~ 30% Myofilament Gene +

Neutral HCM
~ 10%



~ 40% Myofilament Gene +

Bos JM, et al. 2009

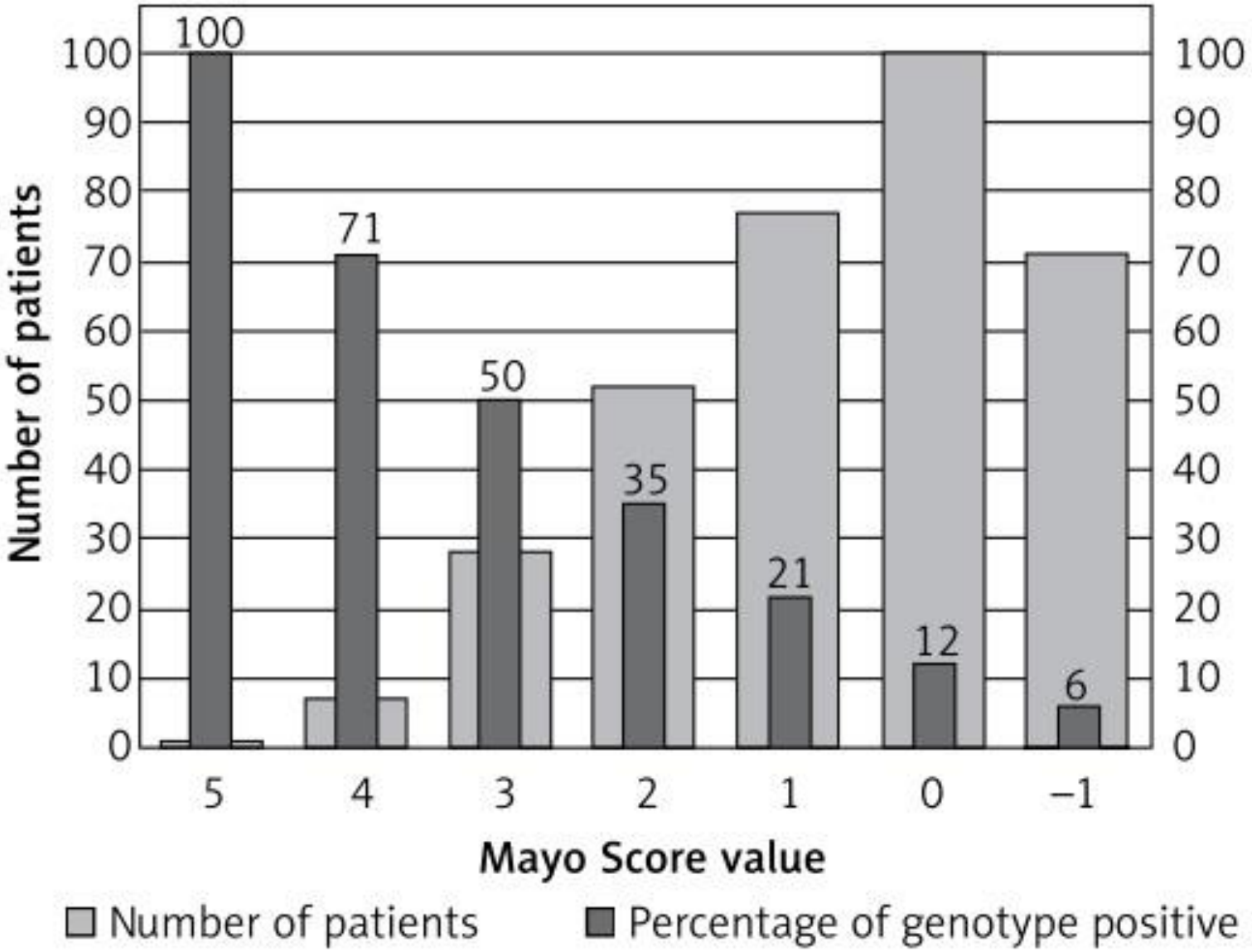


Figure 2. Mayo Score and positive genotype in HCM patients

Bonaventura J, et al. 2018

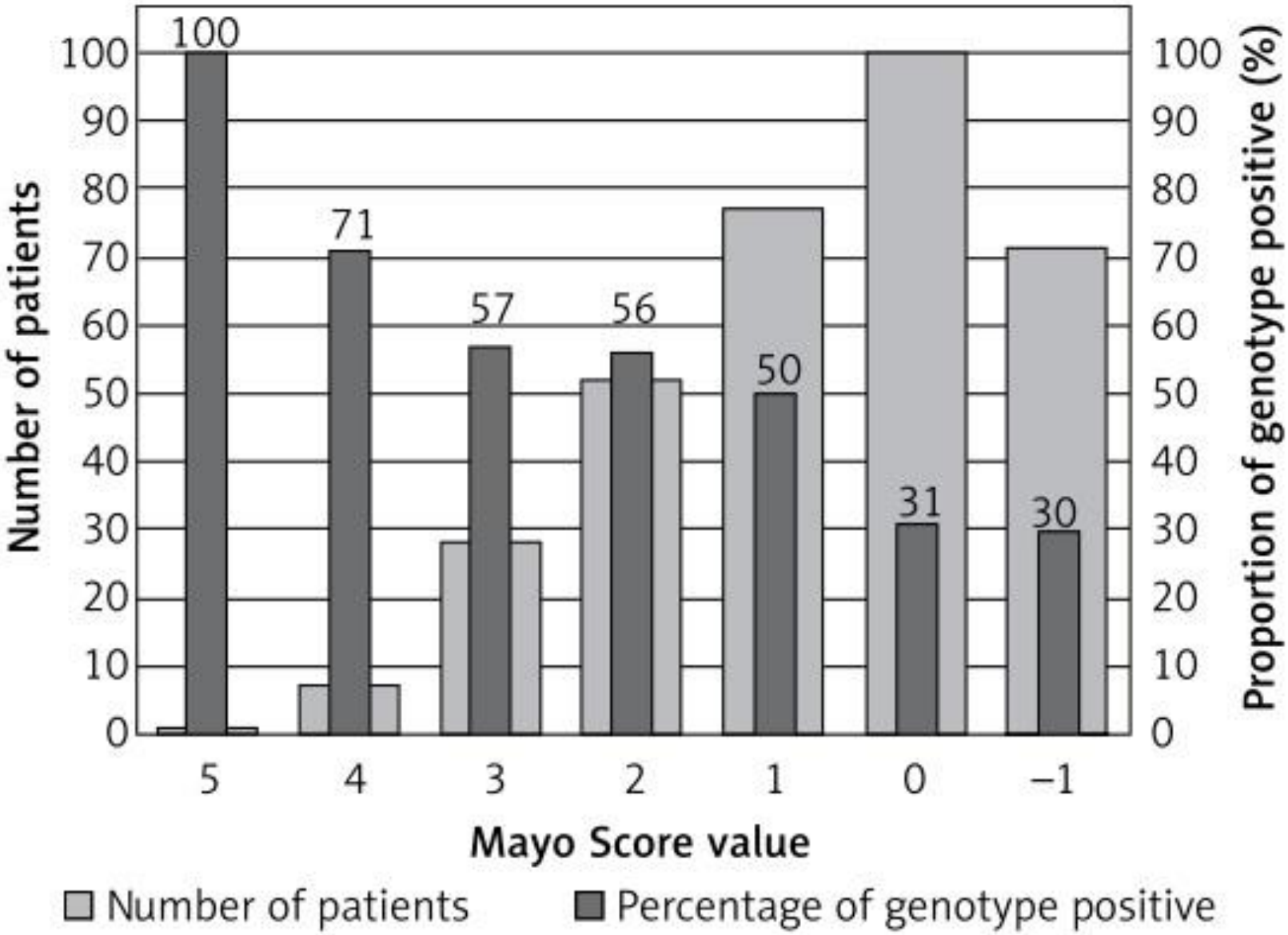


Figure 3. Mayo Score in HCM patients when VUS are considered positive genotype

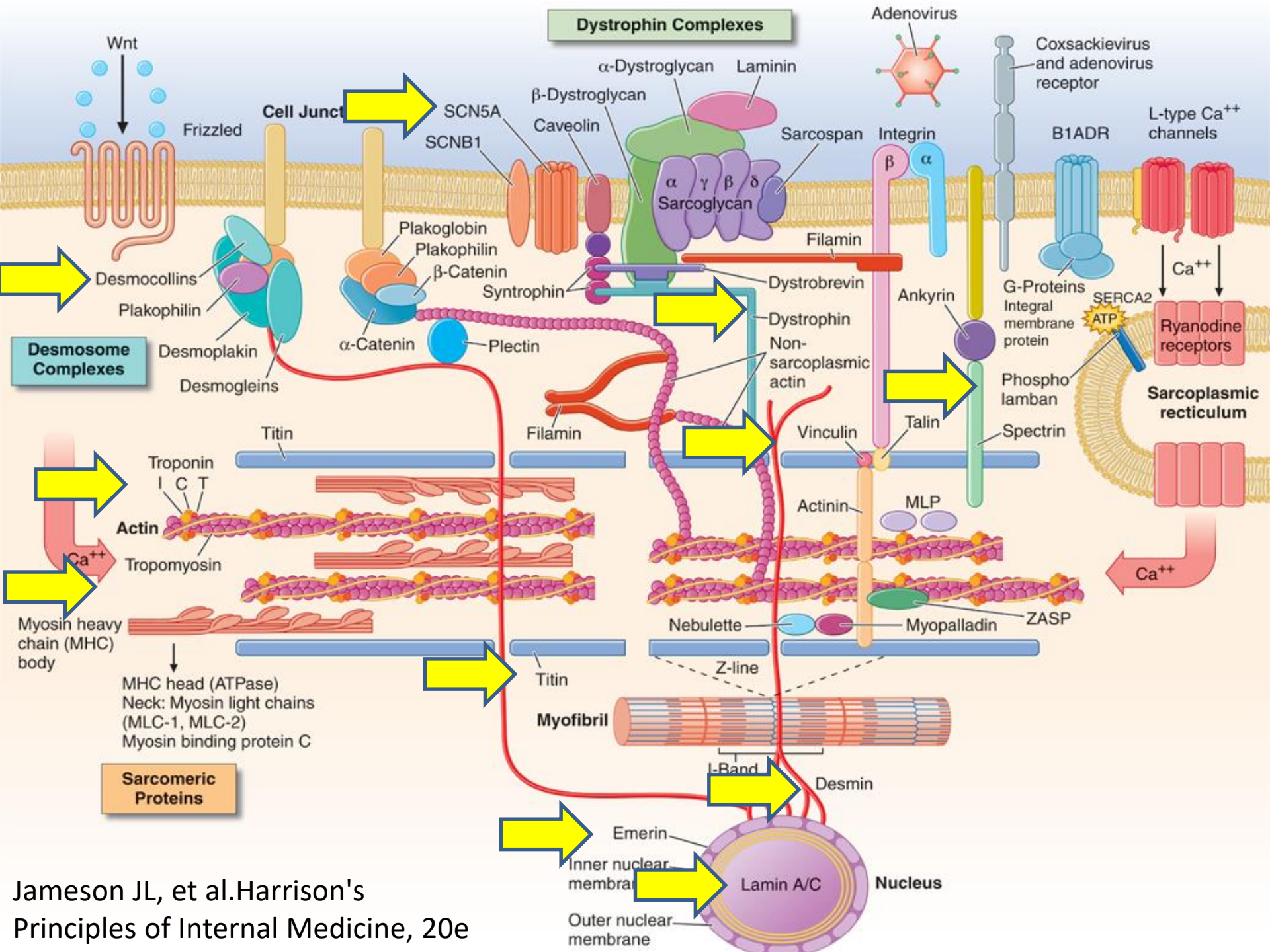
Bonaventura J, et al. 2018

DCM

- Familiární formy tvoří 20-30%
- Mutace více než 30 genů
- Prevalence DCM nejspíše podhodnocená
- Většina AD dědičná
- AR, X-vázaná, mitochondriální dědičnost
- Mendelovská dědičnost je simplifikace
- Mutace v genu pro Lamin A/C (LMNA) zvyšují riziko NS

Gene	Estimated prevalence (%)
TTN	20
MYH7	4–7
LMNA	2–6
SCN5A	2–3
TNNI3	2–3
LDB3	1–3
PLN	1–3
TNNT2	1–3
TNNC1	Rare
TAZ	Rare
CSRP3	Rare
DES	Rare
ACTN2	Rare
ANKRD1	Rare
ABCC9	Rare
TPM1	Rare
DMD	Rare
VCL	Rare
EMD	Rare
MYOZ1	Rare
MYBPC3	Rare
BAG3	Rare
ABCC9	Rare
LAMP2	Rare
EYA4	Rare
TMPO	Rare
PSEN1	Rare
PSEN2	Rare
SGCD	Rare

Ho CY, et al. 2015



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

DCM v klinické praxi

- Idiopatická DCM
- **Vyloučit jinou příčinu** dilatace LK, (PK)
- Detailní rodinná anamnéza (3-4 generace)
- Molekulárně-genetické vyš. probanda

Fenotypy DCM

- **DCM bez převodní poruchy (AD)**
  - 90-95% všech dědičných DCM
  - MYH7, MYH6, TNNT2, TTN, TPM1, TNNC1
- **DCM s převodní poruchou (AD)**
  - LMNA (Emery-Dreifuss muskulární dystrofie)
    - kóduje Lamin A, Lamin C
    - 5-8%, progresivní AV blokády, SVT, SSS, VT, VF
    - NS může být první manifestací choroby
  - SCN5A (též LQTS3, Brugada)
    - 2-3%, AV blokády, SSS, SVT

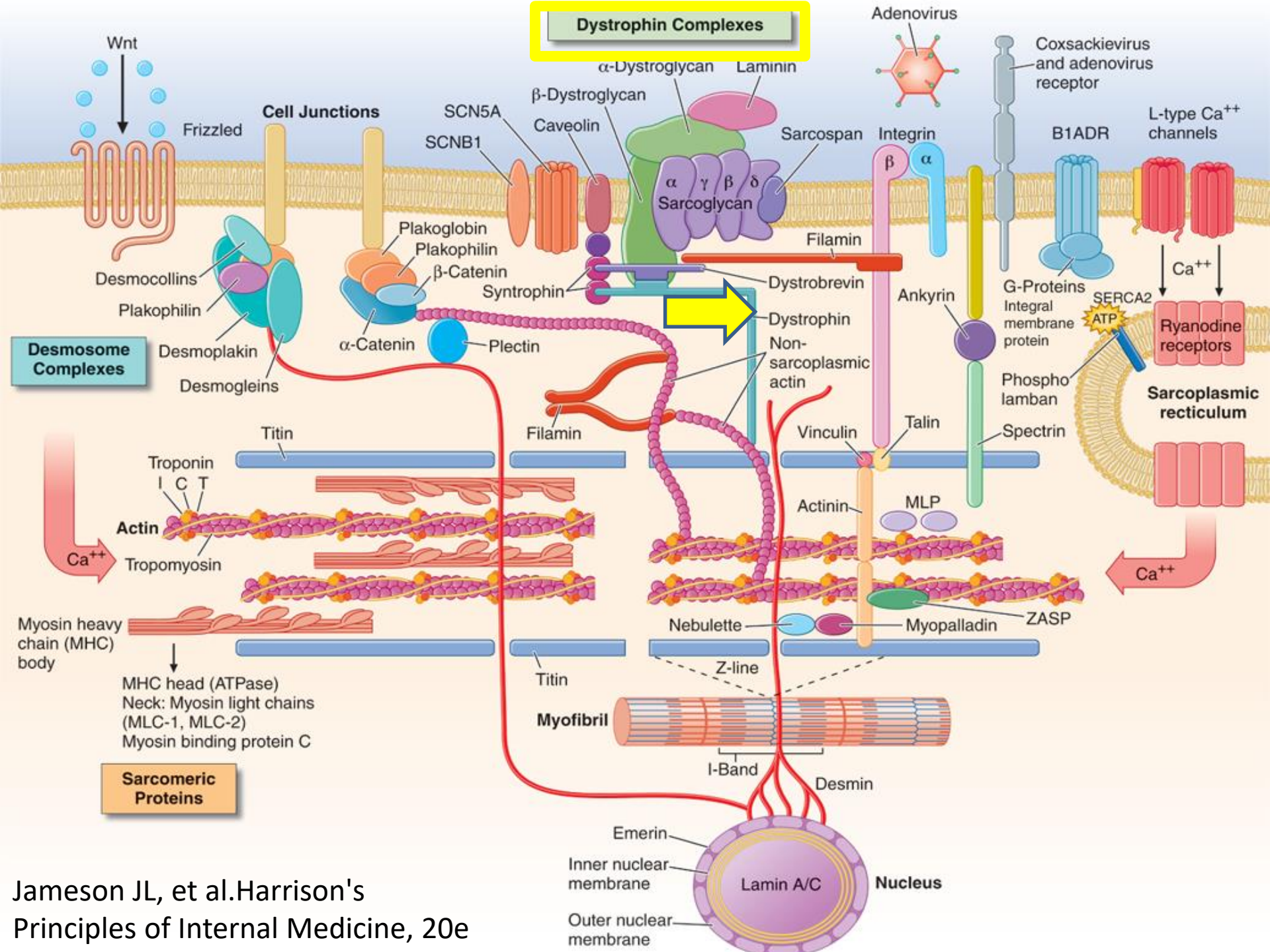
therapy who are expected to survive for >1 year with good functional status.			317, 354
Catheter ablation is recommended in patients with DCM and bundle branch re-entry ventricular tachycardia refractory to medical therapy.	I	B	8,208, 345, 346
An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B	71
Amiodarone should be considered in patients with an ICD that experience recurrent appropriate shocks in spite of optimal device programming.	IIa	C	229
Catheter ablation may be considered in patients with DCM and VA not caused by bundle branch re-entry refractory to medical therapy.	IIb	C	355
Invasive EPS with PVS may be considered for risk stratification of SCD.	IIb	B	115
Amiodarone is not recommended for the treatment of asymptomatic NSVT in	III	A	313,

- **Holter EKG s nsKT**
- **EFLK <45%**
- **Mužské pohlaví**
- **Non-missense mutace**

Priori SG, et al. 2015

Fenotypy DCM

- **DCM s muskulární dystrofií**
  - X- vázaná dědičnost
  - Dystrofin (Duchenne, Becker)



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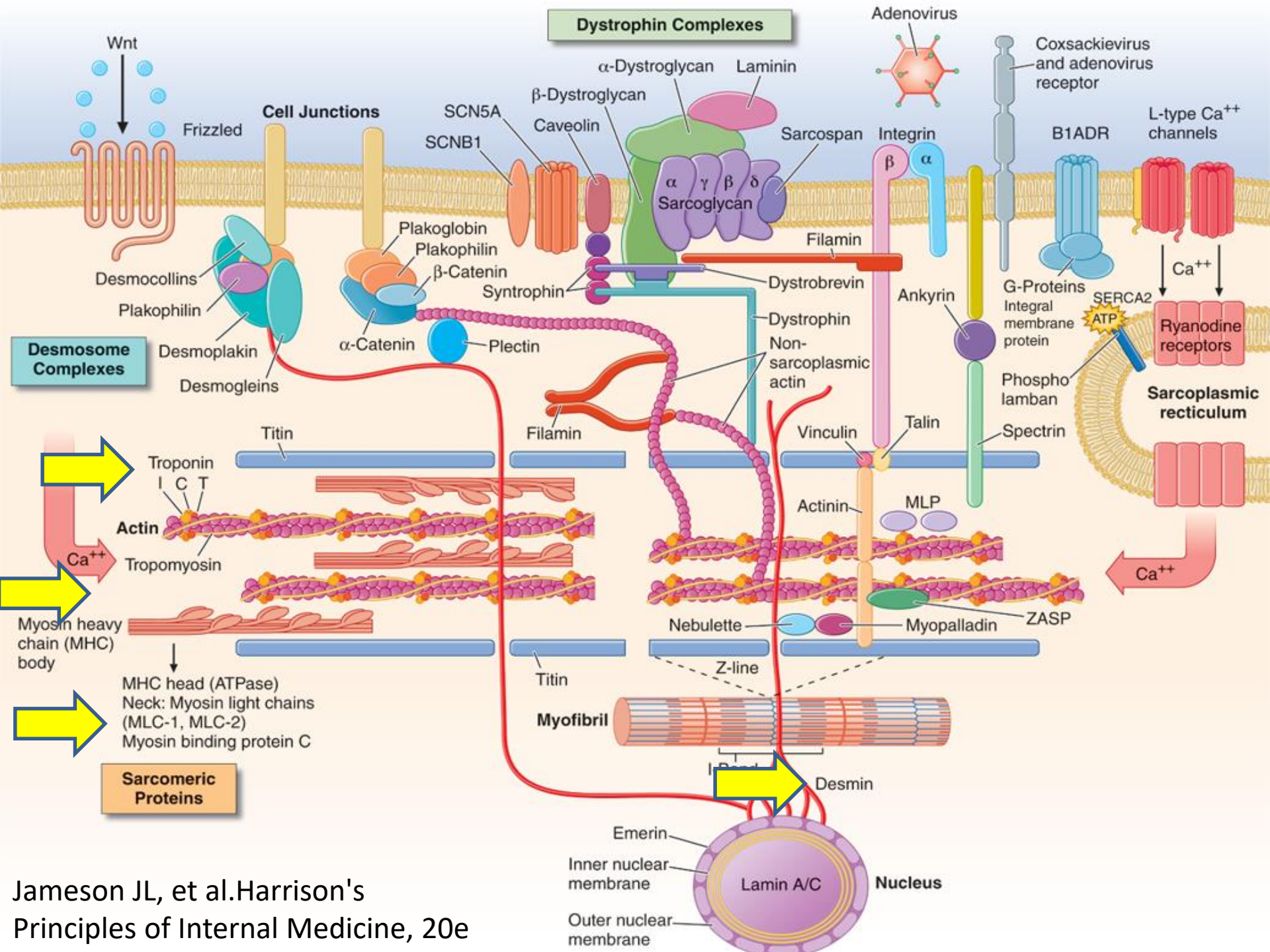
Restriktivní kardiomyopatie

- Troponin I, Troponin T
- Esenciální lehký řetězec myozinu
- Těžký řetězec β-myozinu
- Desmin
- Amyloidóza
  - Transthyretin (RCM + neuropatie)
  - Apolipoprotein A1 (RCM+ nefropatie)
- Hemochromatóza
- Anderson–Fabryho nemoc (GLA)
- Glykogenózy



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ARVC

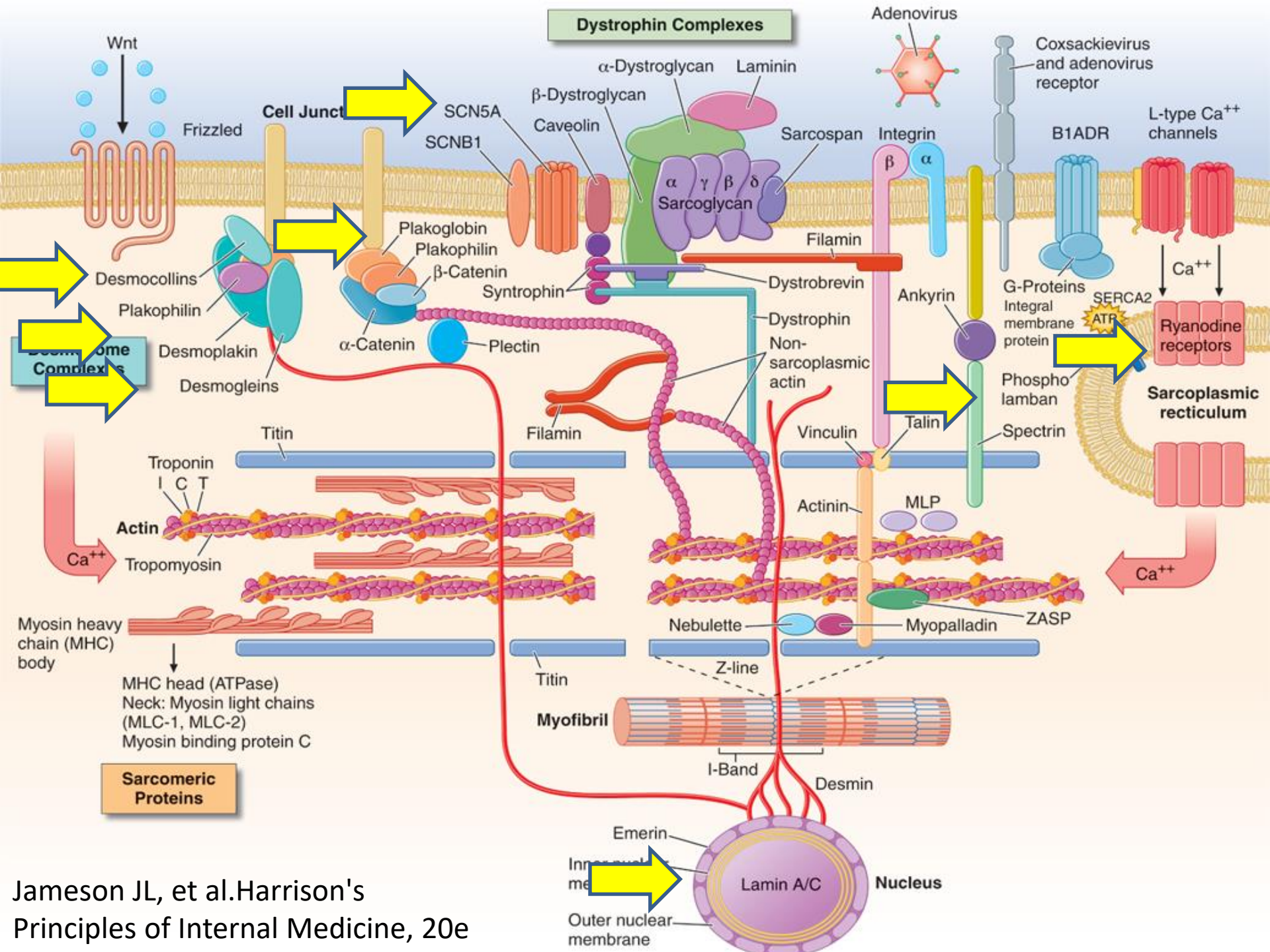
- Cca 30 % je dědičných - zejména AD
- AR – kardiokutánní syndromy
  - 100% penetrance
  - Naxos disease (plakoglobin), Řecko
  - Carvajal syndrome (desmoplakin), Ekvádor, LK

Rampazzo A, et al. 2002

ARVC

- Plakoglobin
- Desmoplakin
- Plakofilin 2
- Desmoglein 2
- Desmokolin 2
- Ryanodinový receptor (katecholaminergní polymorfní KT)
- Transformační růstový faktor β (TGF-β3)
- Transmembránový protein 43 TMEM43
- Lamin A/C
- SCN5A
- Phospholamban

Tiso N, et al. 2001



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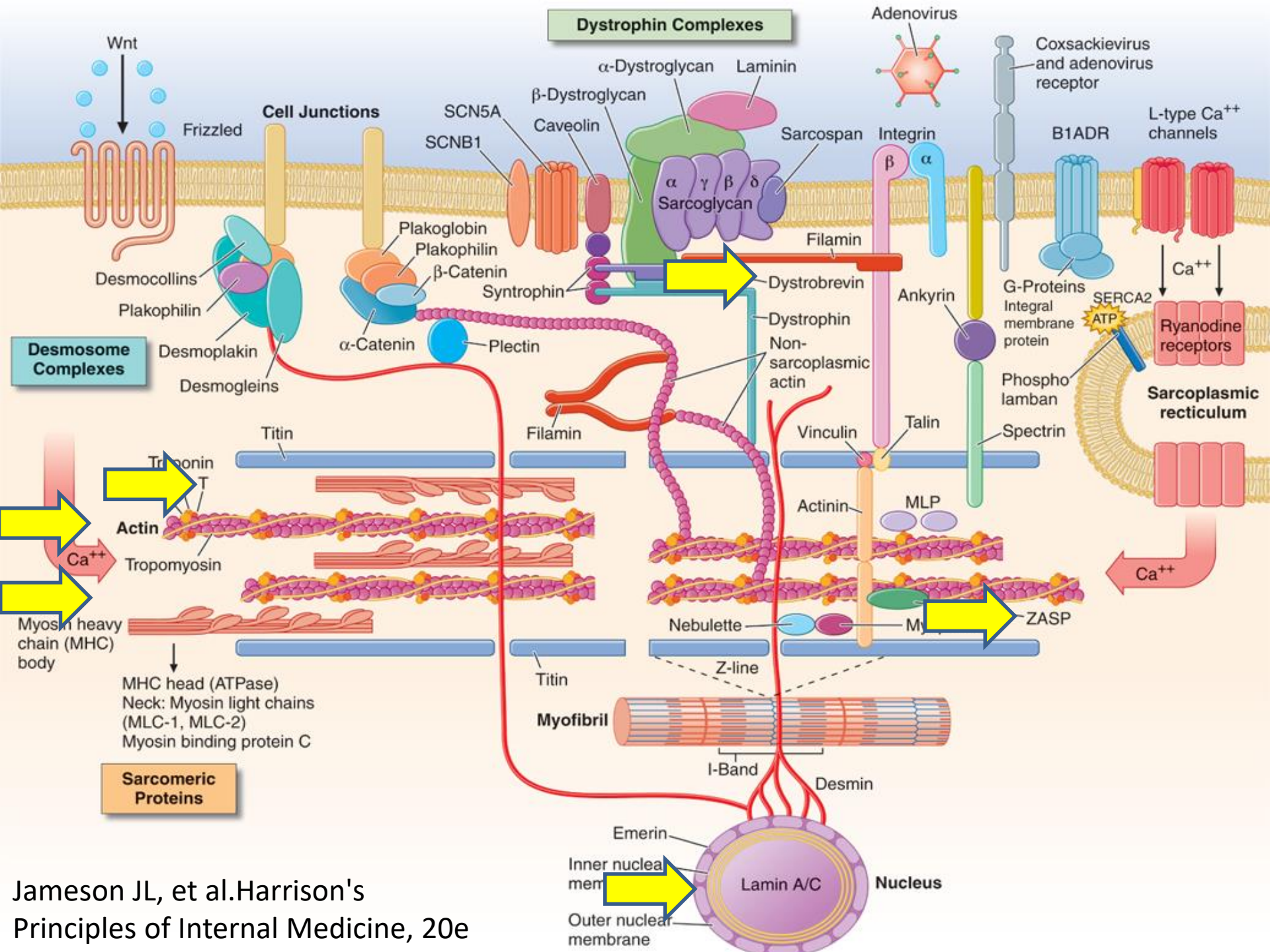
LVNC

- MYH7, ACTC, TNNT2, TNN13, MYBPC3, SCN5A, TPM1…
- α-dystrobrevin
- ZASP (Z-band alternatively spliced protein)
- Lamin A/C
- Taffazin (Barthův syndrom, X-vázaný)

Pignatelli RH, et al. 2003
Bione S, et al. 1997
Ichida F, et al. 2001



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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 ARVC genes are recommended to be included.	10%–40%
ARVC	*DES*, *DSC2*, *DSG2*, *DSP*, *JUP*, *LMNA*, *PKP2*, *PLN*, *RYR2*, *SCN5A*, *TMEM43*, *TTN*†; consider full DCM panel	10%–50%
RCM	Consider HCM or DCM gene panel	10%–60%
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Unknown

Hershberger, et al. 2018

Souhrn

- Některé kardiomyopatie jsou pravděpodobně monogenně podmíněná onemocnění
- AD, AR, X-vázaná i mitochondriální dědičnost
- Genotypová variabilita
- Varianty v genech pro proteiny kardiomyocytů
- Výtěžnost genetického vyšetření je variabilní, lze predikovat u HCM
- Genetické poradenství, klasifikace variant
- Prognostický význam LMNA u DCM