Dilated Cardiomyopathy

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Professor & Chair

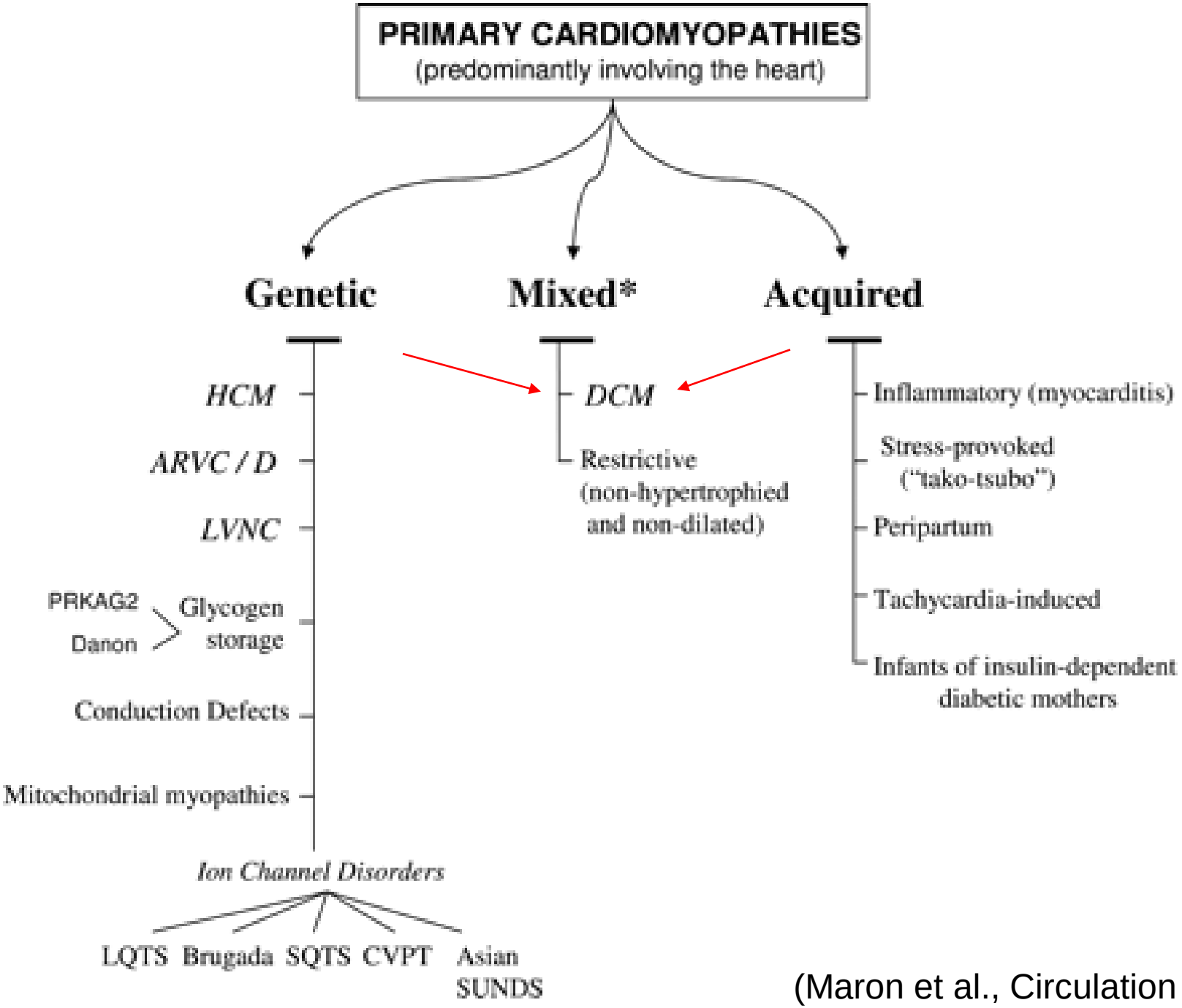
Lecture 2

Cardiomyopathy

- Definition 1: Cardiomyopathy is a **primary** weakening of the heart muscle or a change in heart muscle structure. It is often associated with inadequate heart pumping or other heart function problems.
- Please note: cardiomyopathy is never the result of a disease of the pericardium, of hypertonus, a disease of the coronaries, or a consequence of valve diseases.

Cardiomyopathy

- Definition 2: 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 et al., Circulation 2008).

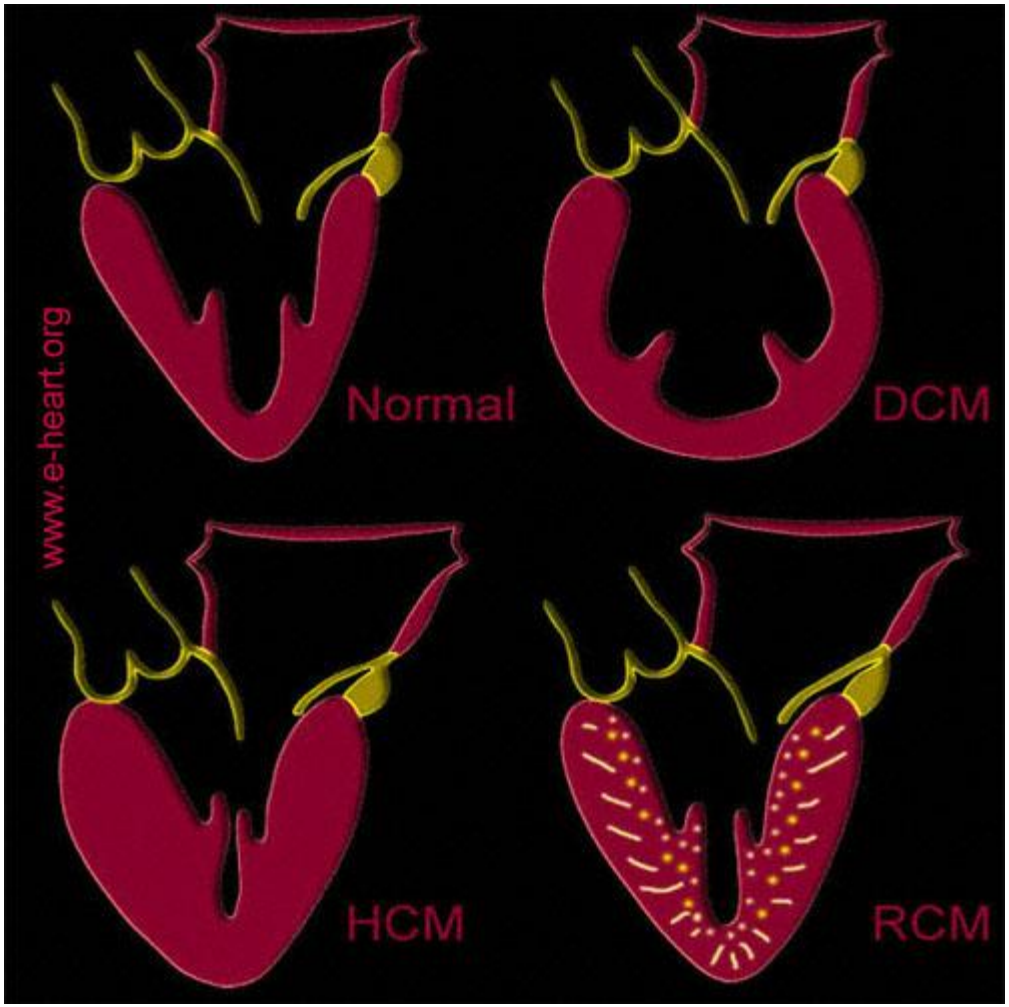


(Maron et al., Circulation 2006)

Most important Cardiomyopathies

- Dilated Cardiomyopathy (DCM)
- Hypertrophic Cardiomyopathy (HCM / HOCM)
- Restrictive Cardiomyopathy (RCM)
- Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D)

(Braunwald, 2005)


www.e-heart.org
Normal
DCM
HCM
RCM

Dilated Cardiomyopathy

- Definition: Dilated cardiomyopathy is a condition in which the heart becomes weakened and enlarged. It cannot pump blood efficiently. Many different medical problems can cause this type of cardiomyopathy.

(Braunwald, 2005)

Cardiomyopathy

- Genetic defects have been shown in many types of cardiomyopathies (but not all).

Dilated Cardiomyopathy (DCM)

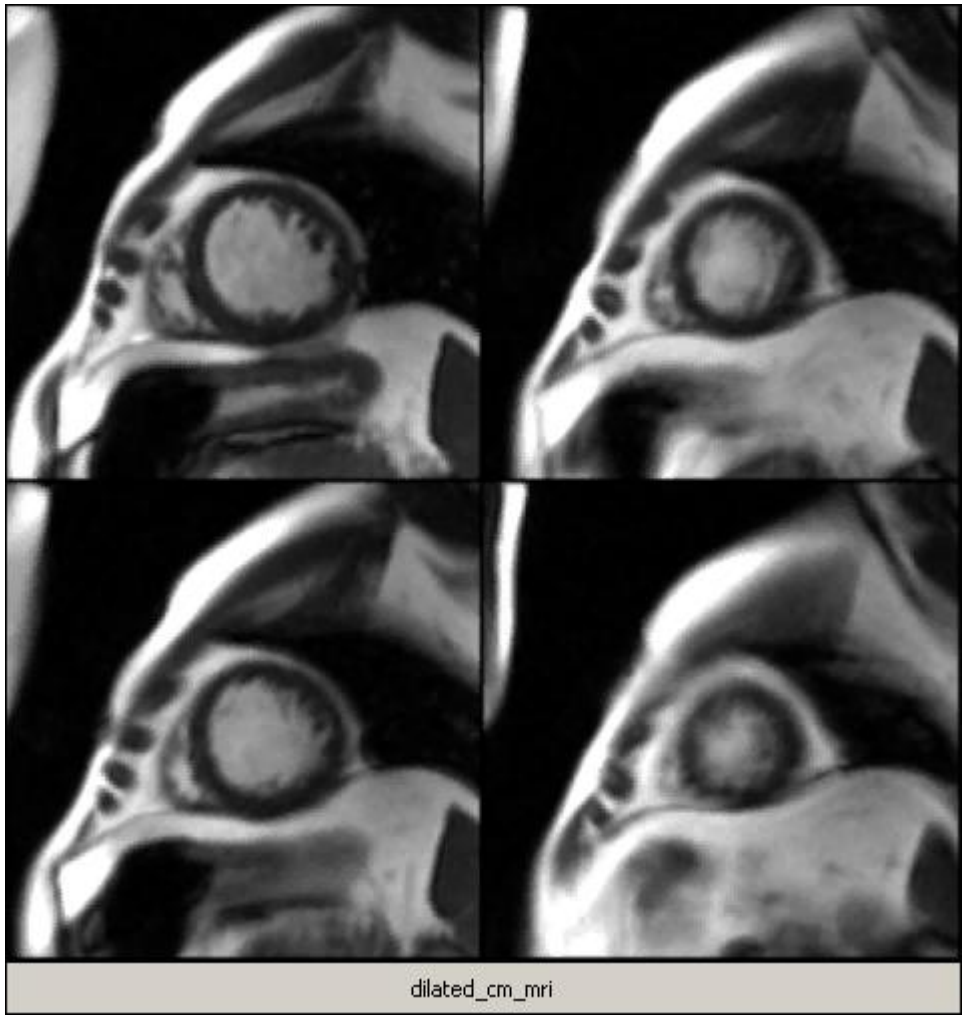
- DCM is characterized by **ventricular chamber enlargement and systolic dysfunction with normal LV wall thickness,** leading to **progressive heart failure** and a **decline in LV contractile function**, **ventricular and supraventriular arrhythmias, conduction system abnormalities, thromboembolism, and sudden or heart failure related death.**
- **Estimated prevalence of 1:2500, most frequent cause of heart transplantation**

(AHA 2006, Maron et al., Circulation)

Dilated Cardiomyopathy - Complications

- Pump failure
- Arrhythmias
- Thromboembolias

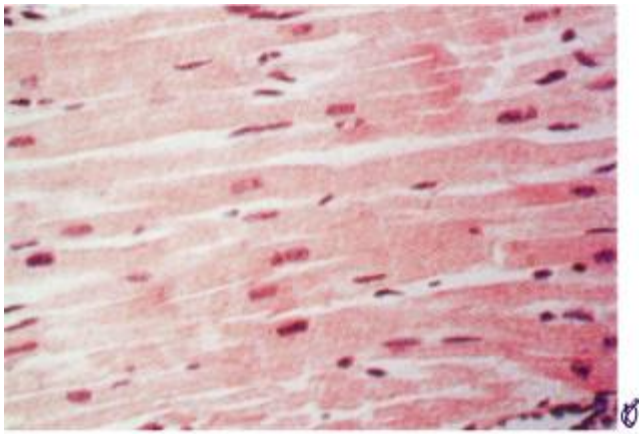
Dilated Cardiomyopathy - dysfunction



Dilated Cardiomyopathy

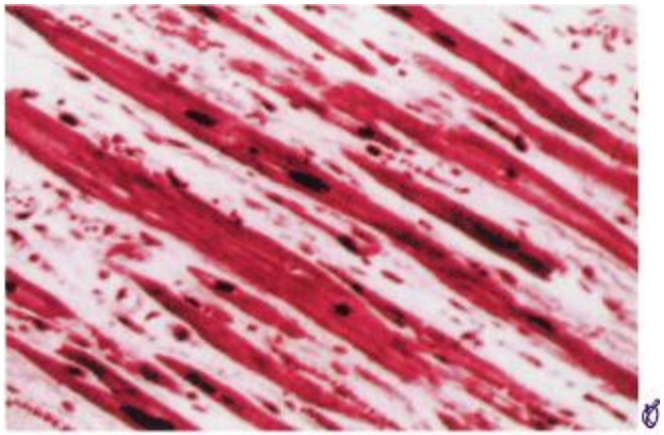
- Pathology: Histology and ultrastructure - not characteristic, but:
  Hypertrophied cardiomyocytes, degenerated cardiomyocytes, interstitial fibrosis

Histology



A

Normal Heart



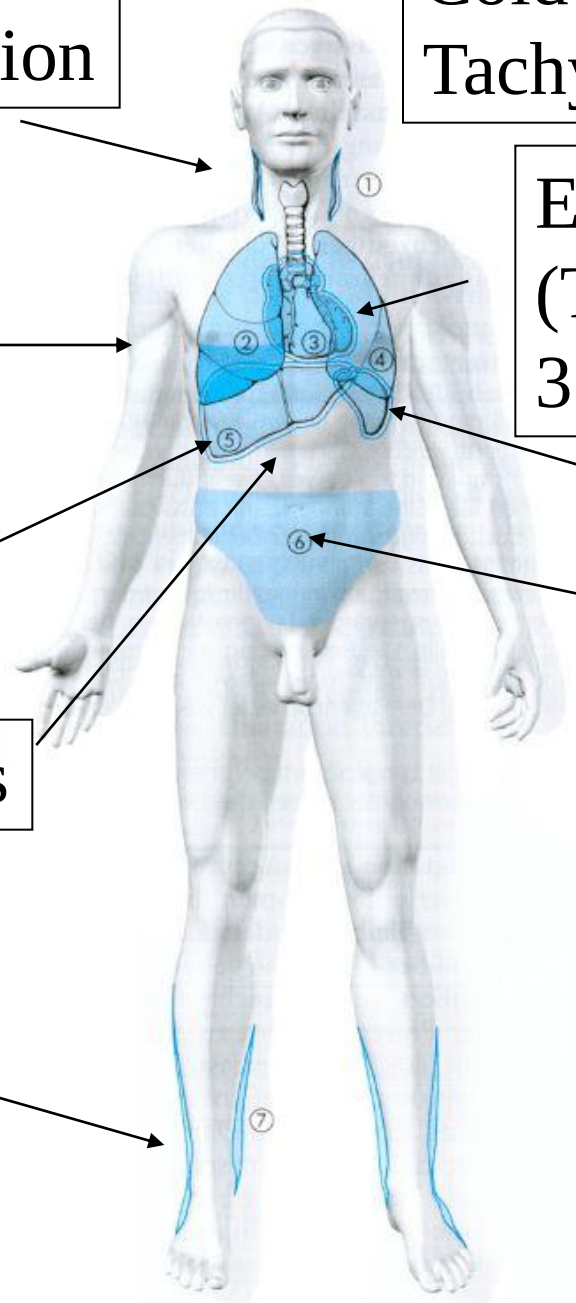
C

DCM Heart

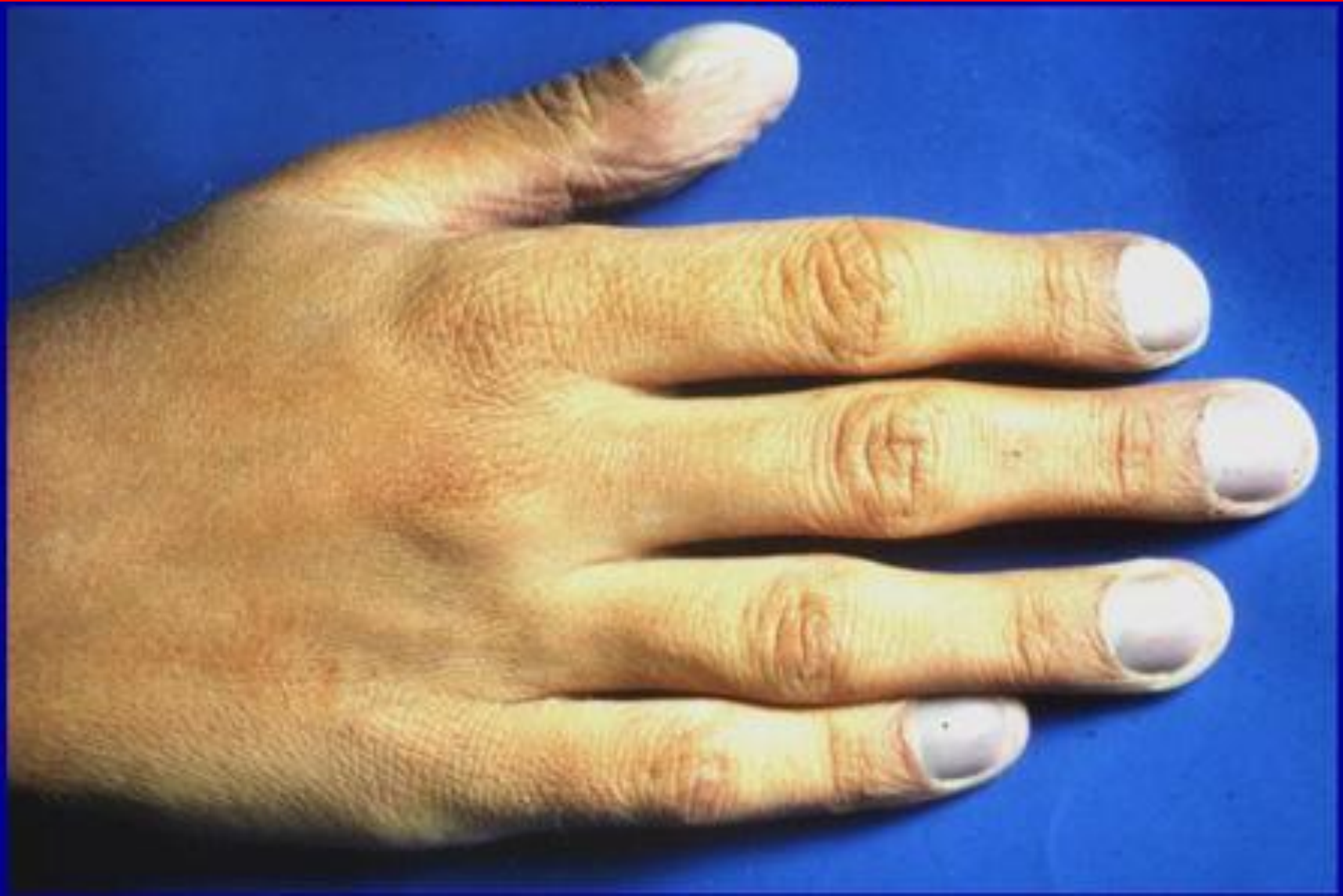
Dilated cardiomyopathy, showing hypertrophy and degeneration of myocytes (dark red) without disarray. There is an increase in interstitial fibrosis (pale pink). Stains: hematoxylin and eosin (From Seidman JG, Seidman C: The genetic basis for cardiomyopathy: From mutation identification to mechanistic paradigms. Cell 104:557, 2001.).

Dilated Cardiomyopathy (DCM)

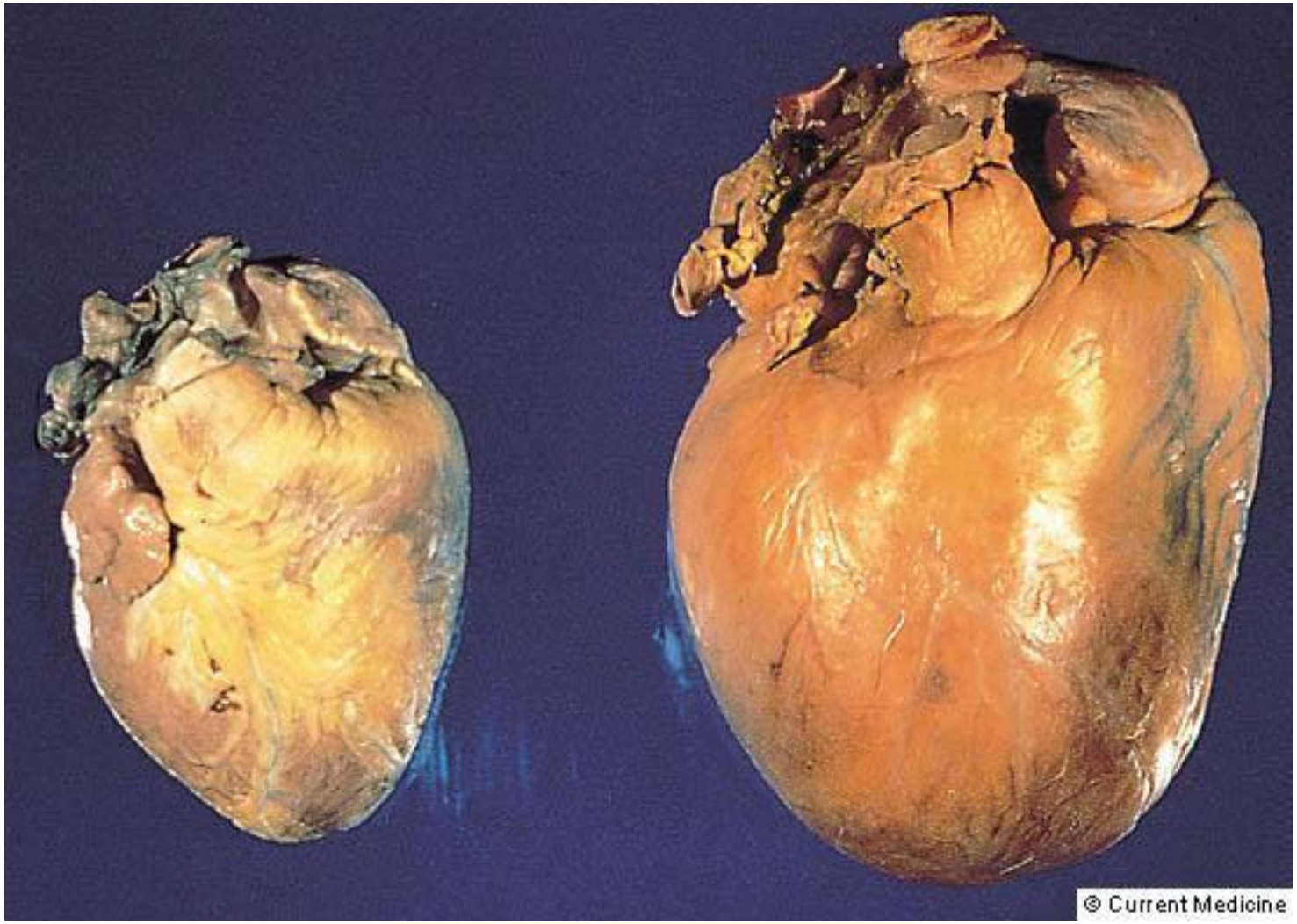
- Frequent Cardiomyopathy (after HCM most frequent)
- Prevalence: up to 40/100 000
- Onset of disease between 20-50 years (or even later in life)
- Variable Penetrance
- Symptoms of progressive Heart Failure and Arrhythmias


Neck vein congestion
Cold-Sweat, Orthopnoe, Tachypnoe, Cyanosis
Enlarged Heart (Tachycardia, 3. Heart sound)
Lung congestion
Pulmonary edema
Congestion of the liver
Ascites, Anasarca
Appetite loss
Lung – symptoms in Heart Failure: “Asthma cardiale”
Edema

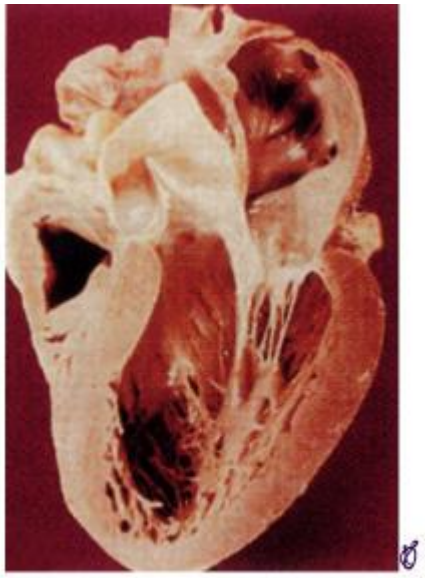
Nail clubbing, Drumstick fingers (Hippocratic fingers)
Associated with a number of diseases –
mostly of the heart and lungs



Gross pathology

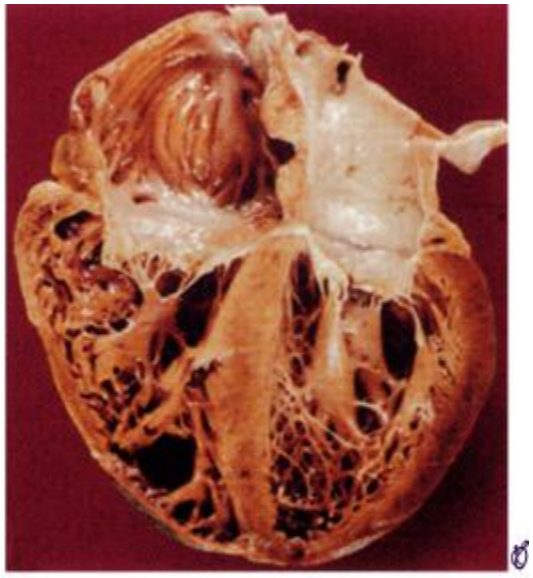


Dilated Cardiomyopathy (DCM)



B

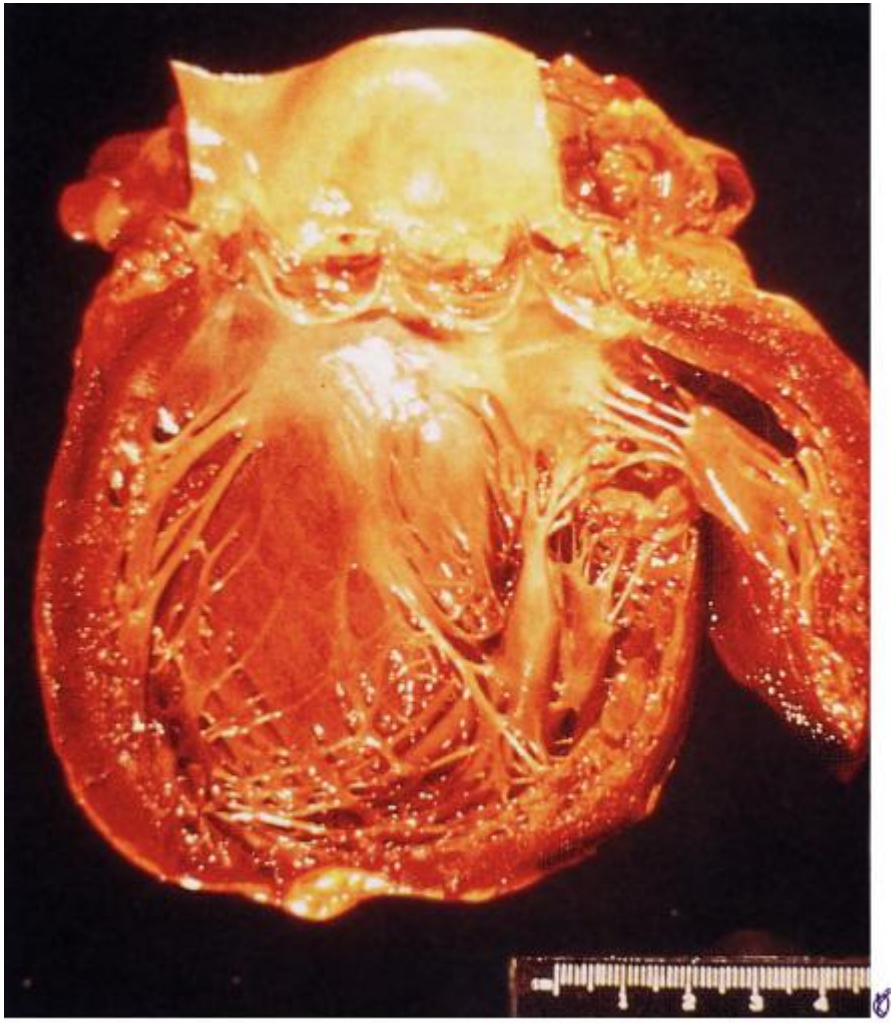
Normal Heart



C

DCM Heart

DCM – secondary changes (globular geometry)

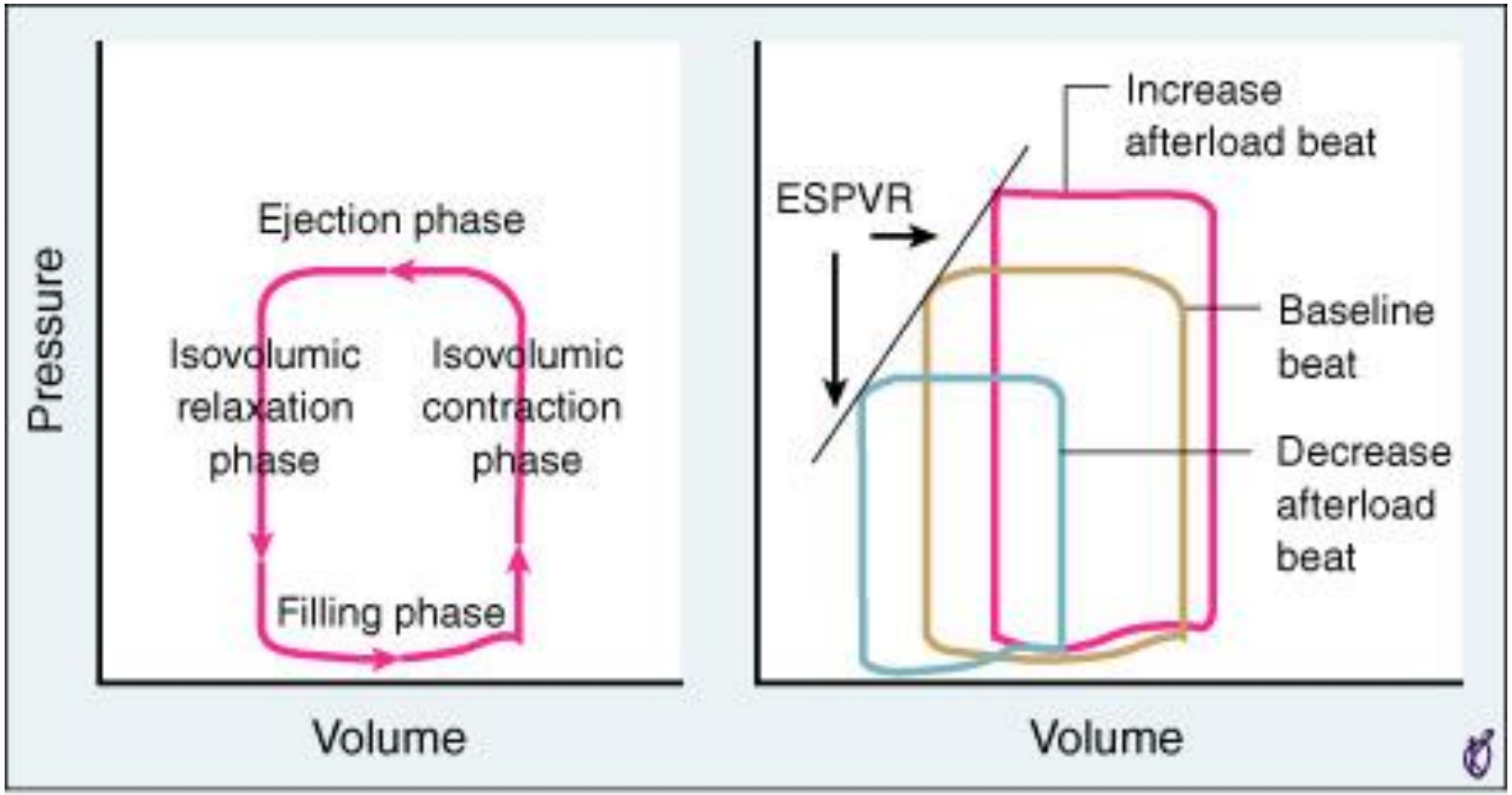


Gross pathology of dilated cardiomyopathy. Prominent ventricular dilatation is apparent in this heart, which has been opened so that the interior of the left ventricle can be seen. **Wall thickness is normal**, but the shape of the heart has become **more globular**. (From Kasper EK, Hruban RH, Baughman KL: Idiopathic dilated cardiomyopathy. *In* Abelmann WH, Braunwald E [eds.]. Atlas of Heart Diseases. Vol 2. Cardiomyopathies, Myocarditis, and Pericardial Disease. Philadelphia, Current Medicine, 1995, pp 3.1–3.18.)

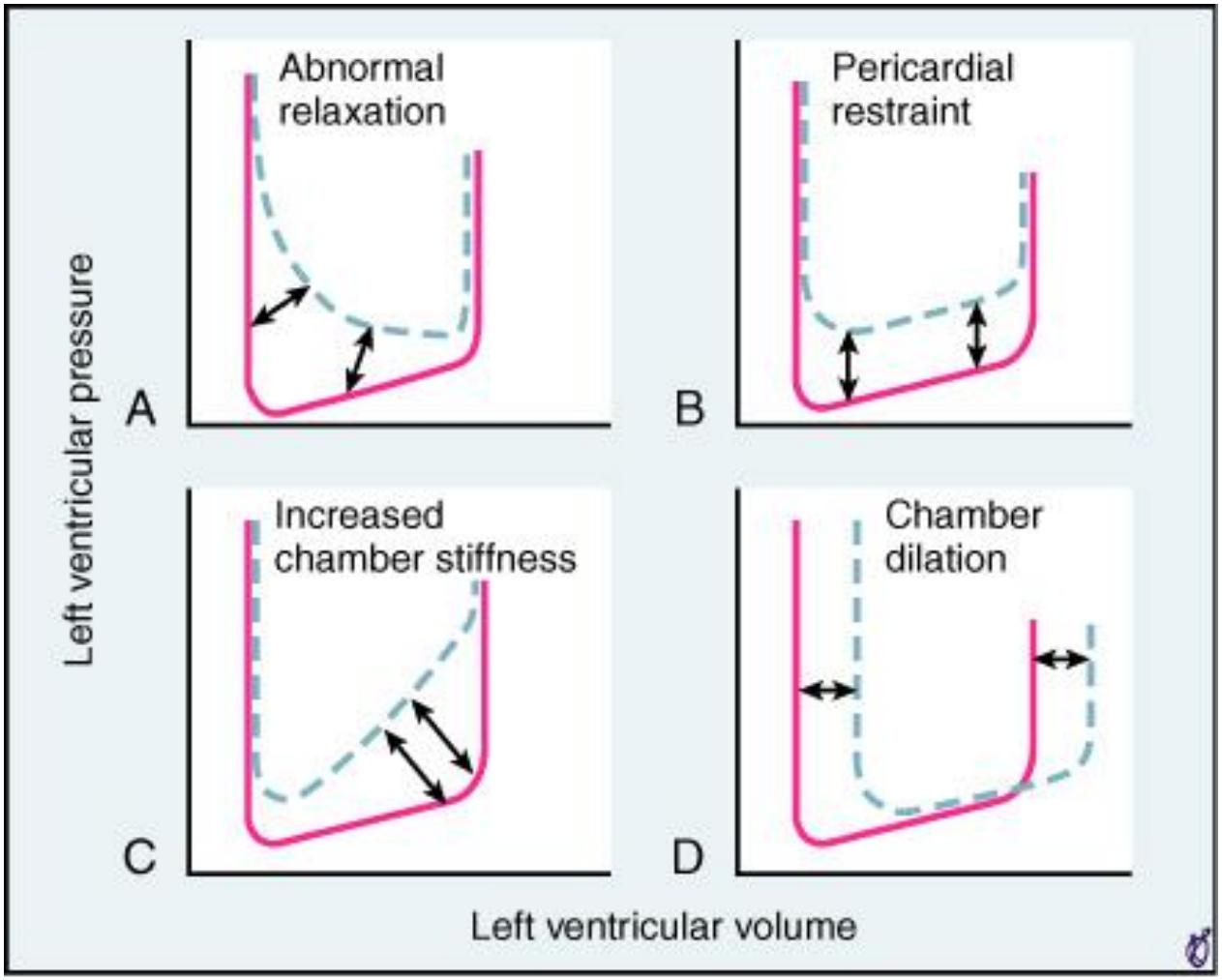
TABLE 20–2 Definitions of Terms Used to Describe Systolic and Diastolic Function

Term	Definition
Preload	Distending force of the ventricular wall, which is highest at end-diastole and is responsible for sarcomere length at the beginning of systolic contraction
Afterload	Resisting force of the ventricular wall during systolic ejection, which is necessary to overcome peripheral vascular resistance or impedance; measures of afterload are peak-systolic, mean-systolic, or end-systolic wall stress
Contractility	Intrinsic ability of the myocardium to generate force at a certain rate and time (controlled for loading conditions)
Cardiac output	Stroke volume multiplied by heart rate
Stroke work	Mean systolic blood pressure multiplied by stroke volume
Stroke force	Stroke work per ejection time
Stress	Force per area
Wall stress	Pressure multiplied by radius, divided by wall thickness × 2
Compliance or distensibility	Change in volume per change in pressure (dV/dP)
Elastance	Slope of the end-systolic pressure-volume relation
Elasticity	Property of a material to restore its initial length or geometry after distending force has been removed
Strain	Length change in percent of initial length; two definitions are used: LaGrangian strain $e = (l - l_o)l_o$ and natural strain $e = \ln(l/lo)$
Stiffness	Pressure per volume change (dP/dV). *Ventricular stiffness* is a measure for changes of the ventricle as a whole; *myocardial stiffness* is a measure for changes of the myocardium itself. Ventricular properties are characterized by instantaneous pressure-volume relations, whereas myocardial properties are best described by stress-strain relations.
Creep	Time-dependent lengthening of a material in the presence of a constant force
Stress relaxation	Time-dependent decrease of stress in the presence of a constant length
Viscoelasticity	Resistance of a material to length changes (strain) or the velocity of length changes (strain rate)

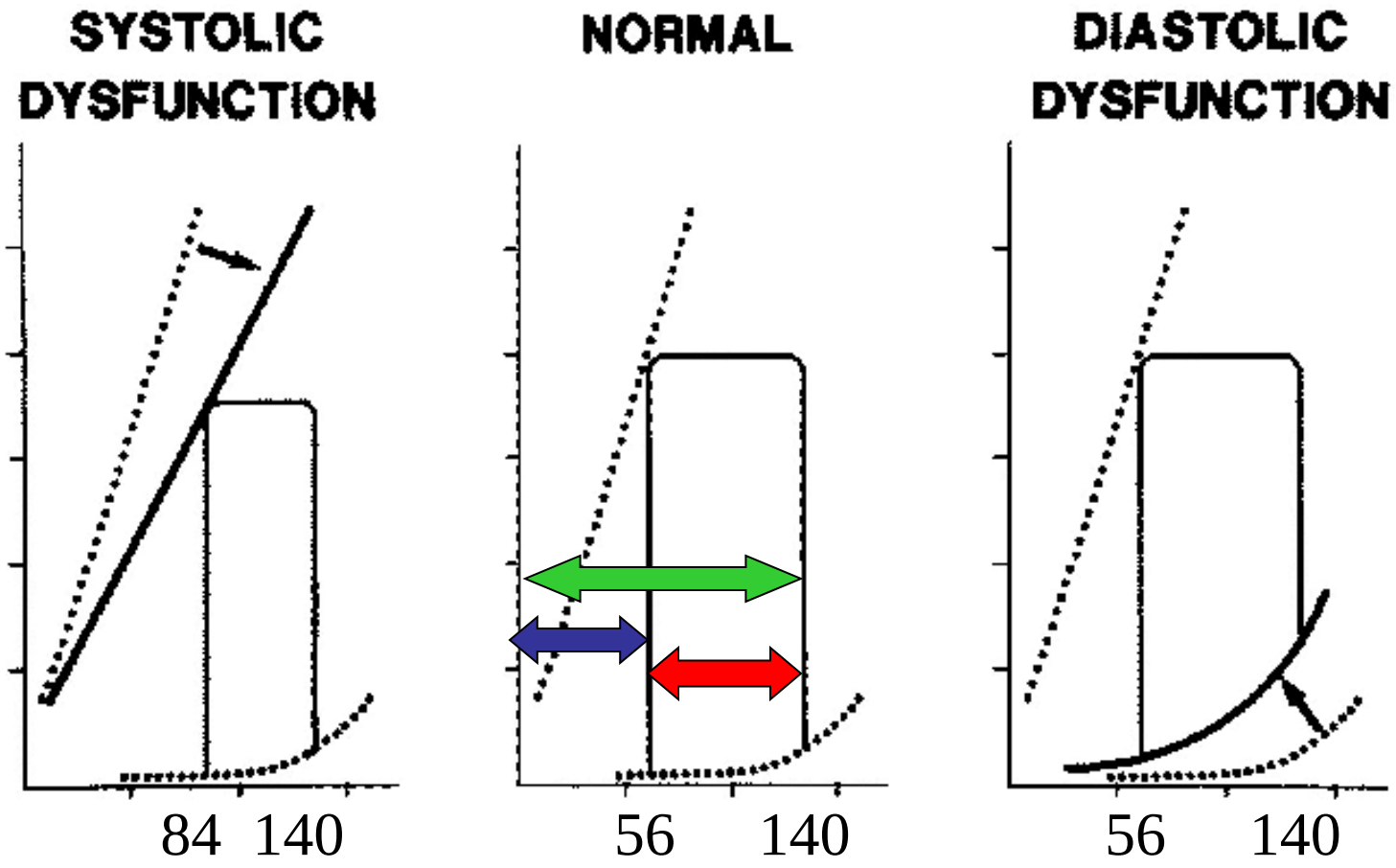
Physiology


Pressure
Ejection phase
Isovolumic relaxation phase
Isovolumic contraction phase
Filling phase
Volume
ESPVR
Increase afterload beat
Baseline beat
Decrease afterload beat
Volume

Types of heart failure



Systolic and Diastolic Heart Failure



Ejektionfraction (EF) = SV/EDV oder EDV-ESV/EDV

Hier: EF = 140 – 56 / 140 = 84 / 140 = 0,6 or 60%

(SV = Stroke Volume, EDV = enddiastolic Volume, ESV = endsystolic Volume)

Large enddiastolic volumes (chronic enlarged heart) do cause difficult working conditions - WHY?

- **Law of Laplace (Walltension):**

$$T = pr / 2d$$

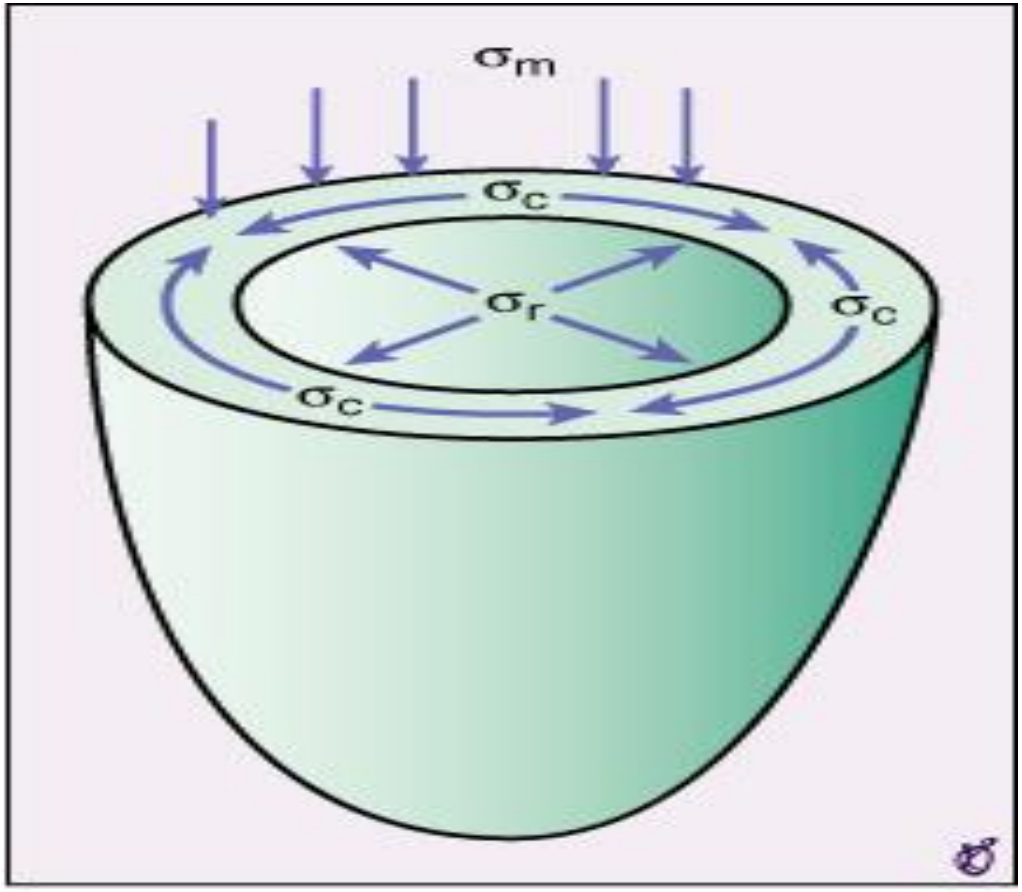
p = pressure
r = radius
d = Wall thickness of ventricle
T = Walltension

Larger diameters (as indicated by large radius) cause increased walltension and as such cause stress to the myocardium (increase of oxygen demand)

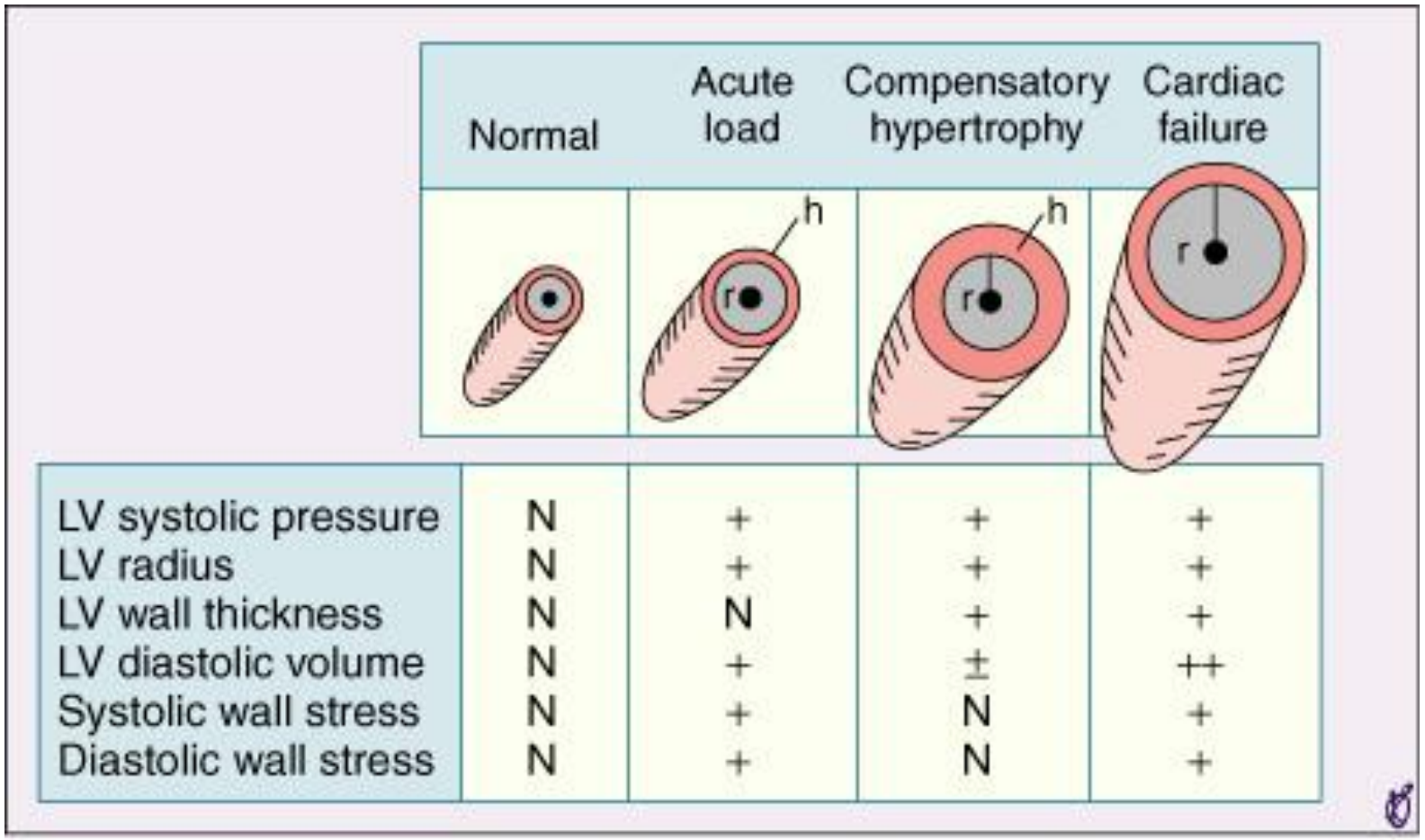
As such it has been hypothesized that hypertrophy is the response of the myocardium to increased walltension (i. e. thicker ventricular walls normalize walltension).

The concept of wall tension

Circumferential (σc), meridional (σm), and radial (σr) components of left ventricular wall stress from an ellipsoid model. The three components of wall stress are mutually perpendicular. (From Fifer MA, Grossman W: Measurement of ventricular volumes, ejection fraction, mass, and wall stress. In Grossman W [ed]: Cardiac Catheterization and Angiography. 5th ed. Philadelphia, Lea & Febiger, 1996, p 34.)



Wall tension – progression of disease



	Normal	Acute load	Compensatory hypertrophy	Cardiac failure
LV systolic pressure	N	+	+	+
LV radius	N	+	+	+
LV wall thickness	N	N	+	+
LV diastolic volume	N	+	±	++
Systolic wall stress	N	+	N	+
Diastolic wall stress	N	+	N	+

Wall tension – progression of disease

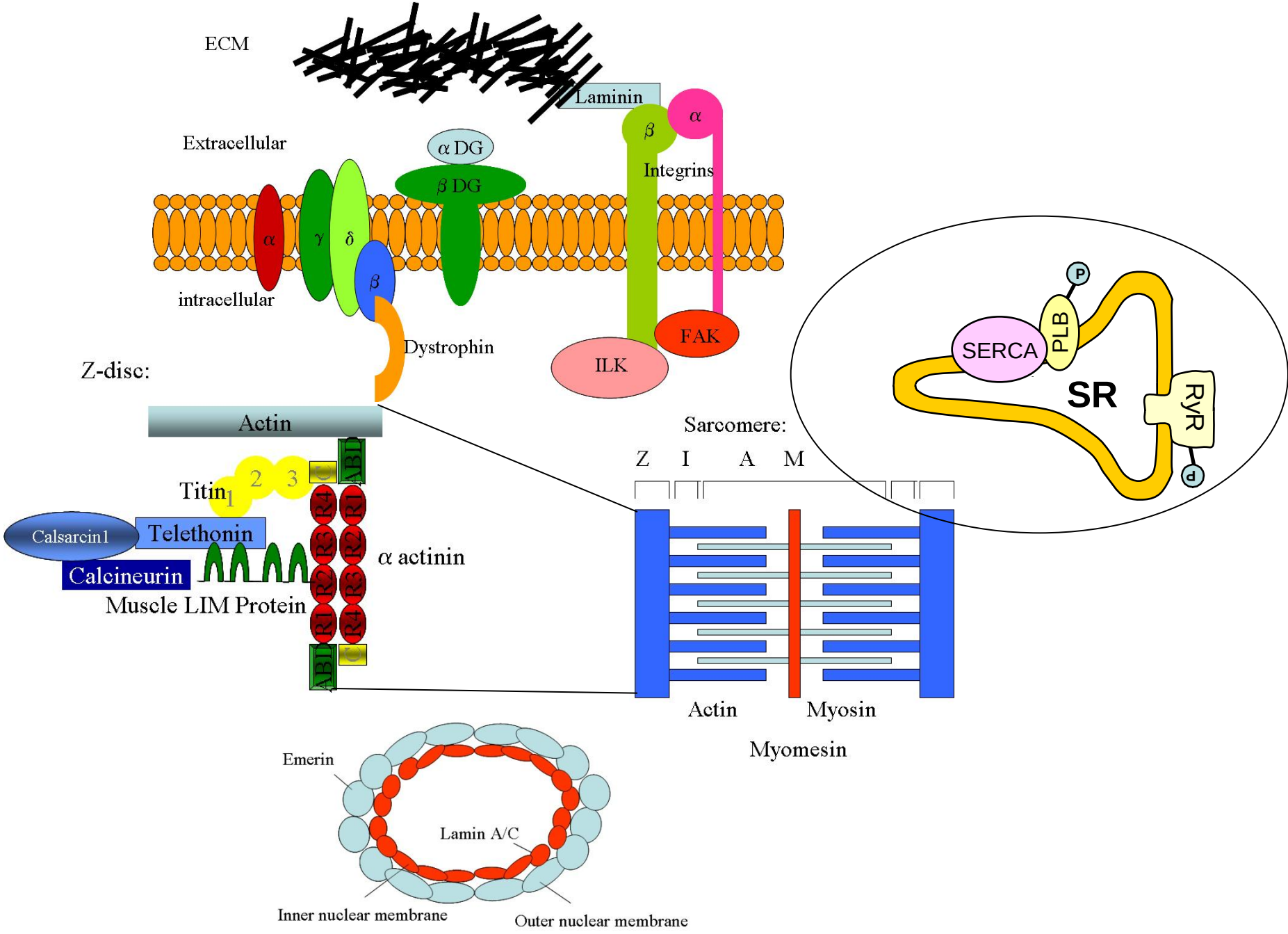
- But how is wall tension translated into myocardial hypertrophy?
- Mechanosensation: the ultimate process of “sensing” and “translating” of a mechanical stimulus into a biochemical signal.
- Mechanosensation and mechano-transduction involve a variety of different molecules and intracellular systems such as integrins, the Z-disk and titin kinase.

Secondary Cardiomyopathies
Infiltrative*
Amyloidosis (primary, familial autosomal dominant†, 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)
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†
Nutritional deficiencies
Beriberi (thiamine), 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

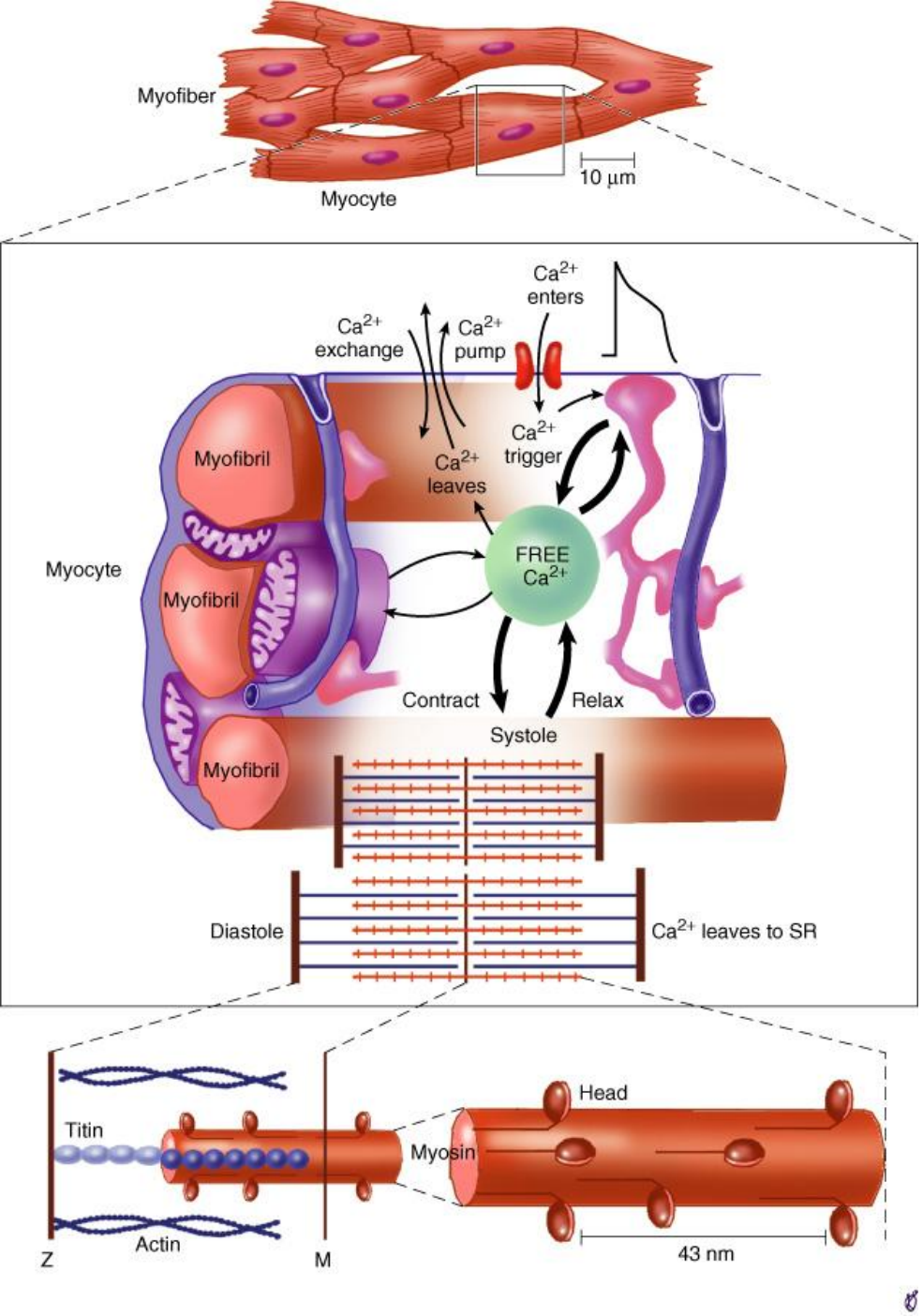
*Accumulation of abnormal substances between myocytes (ie, extracellular).
†Genetic (familial) origin.
‡Accumulation of abnormal substances within myocytes (ie, intracellular).

Characteristics of DCM Genes

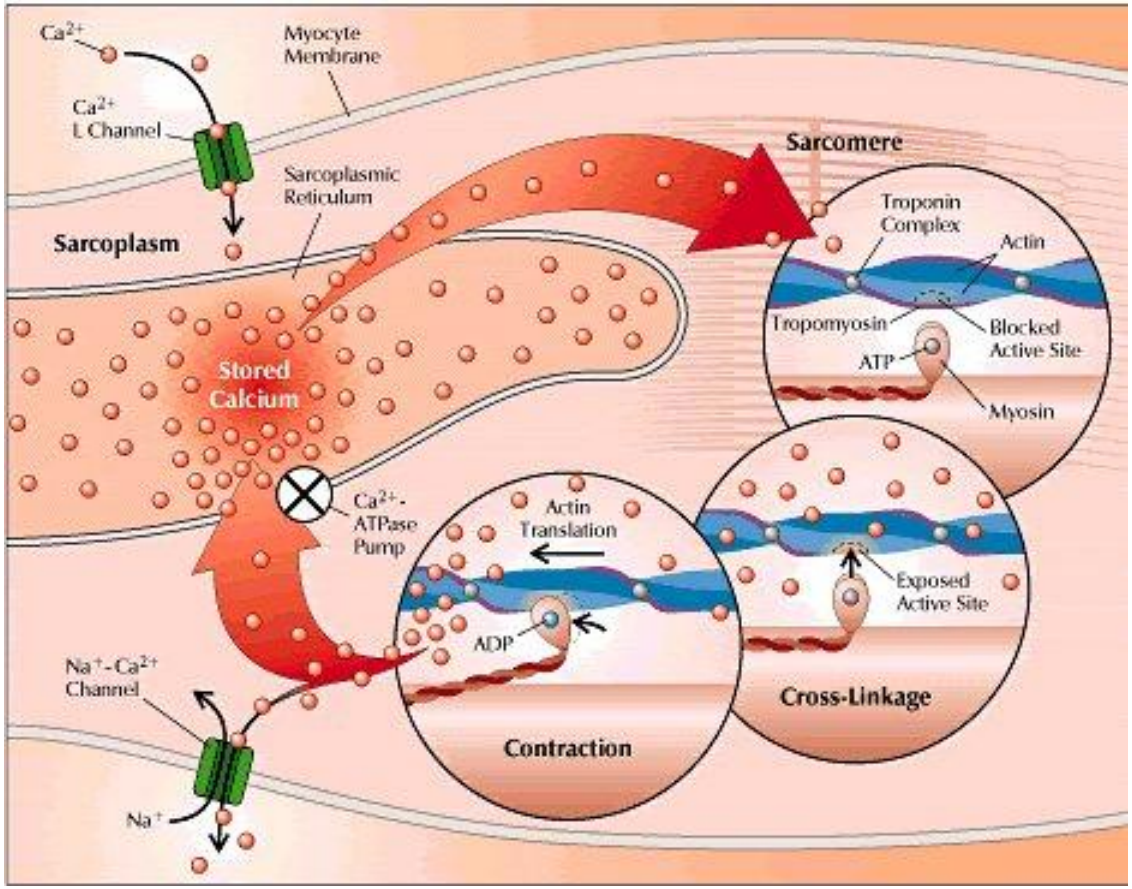
- Variable penetrance
- Age dependent onset of disease (midlife, 3., 4. decade of life or even later)
- Disease genes have only been detected in about 10 -20 % of familial cases: it is expected that more disease genes will be identified
- Monogenic disease versus polygenic disease


ECM
Laminin
α
β
Integrins
Extracellular
α DG
β DG
α
γ
δ
β
intracellular
Dystrophin
FAK
ILK
Z-disc:
Actin
Titin
1
2
3
ABD
R1
R2
R3
R4
Calsarcin1
Telethonin
Calcineurin
Muscle LIM Protein
α actinin
Sarcomere:
Z
I
A
M
Actin
Myosin
Myomesin
P
PLB
SERCA
SR
RyR
Emerin
Lamin A/C
Inner nuclear membrane
Outer nuclear membrane

Electro-mechanical coupling

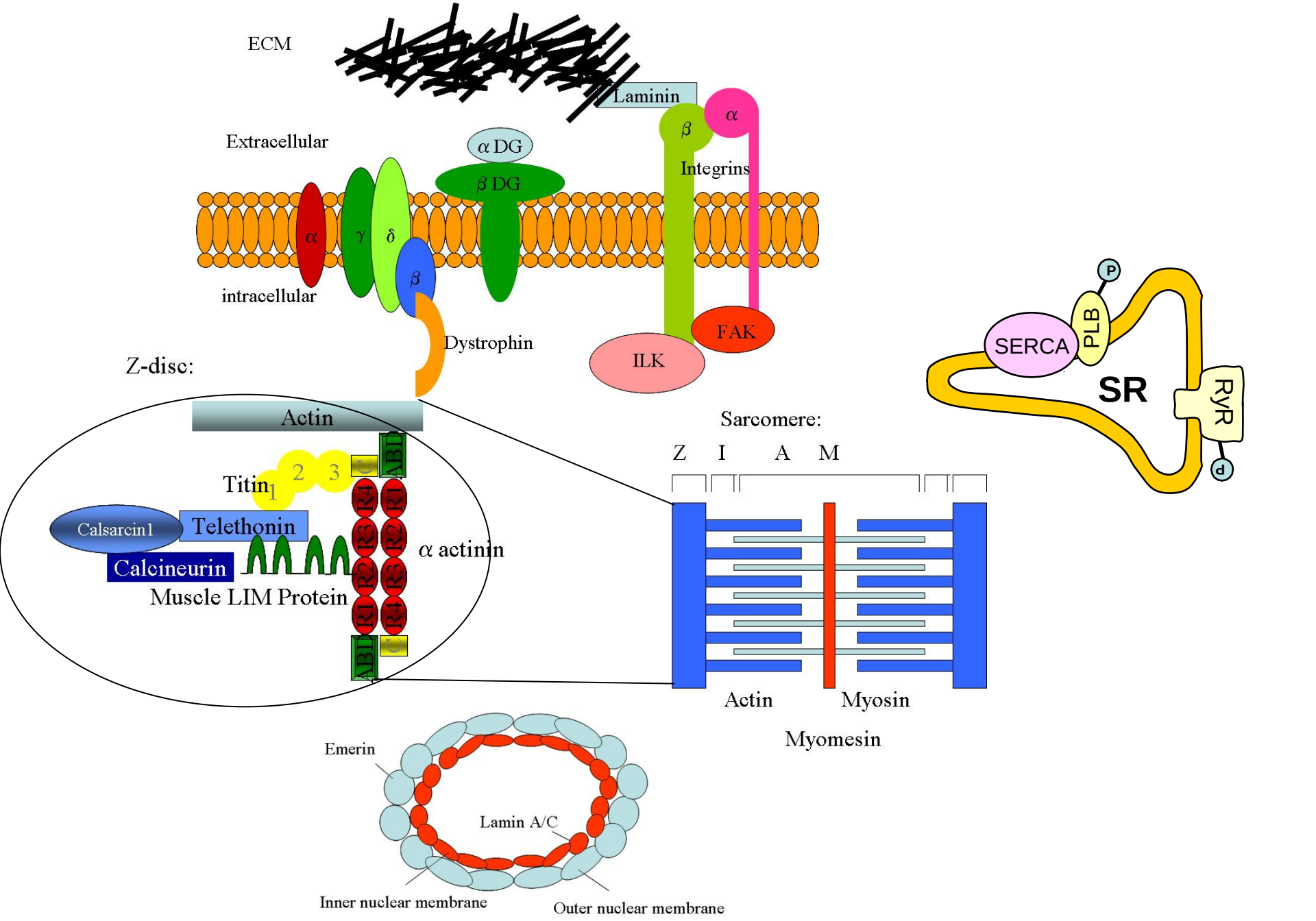


Sarcoplasmic Reticulum ATPase (SERCA)

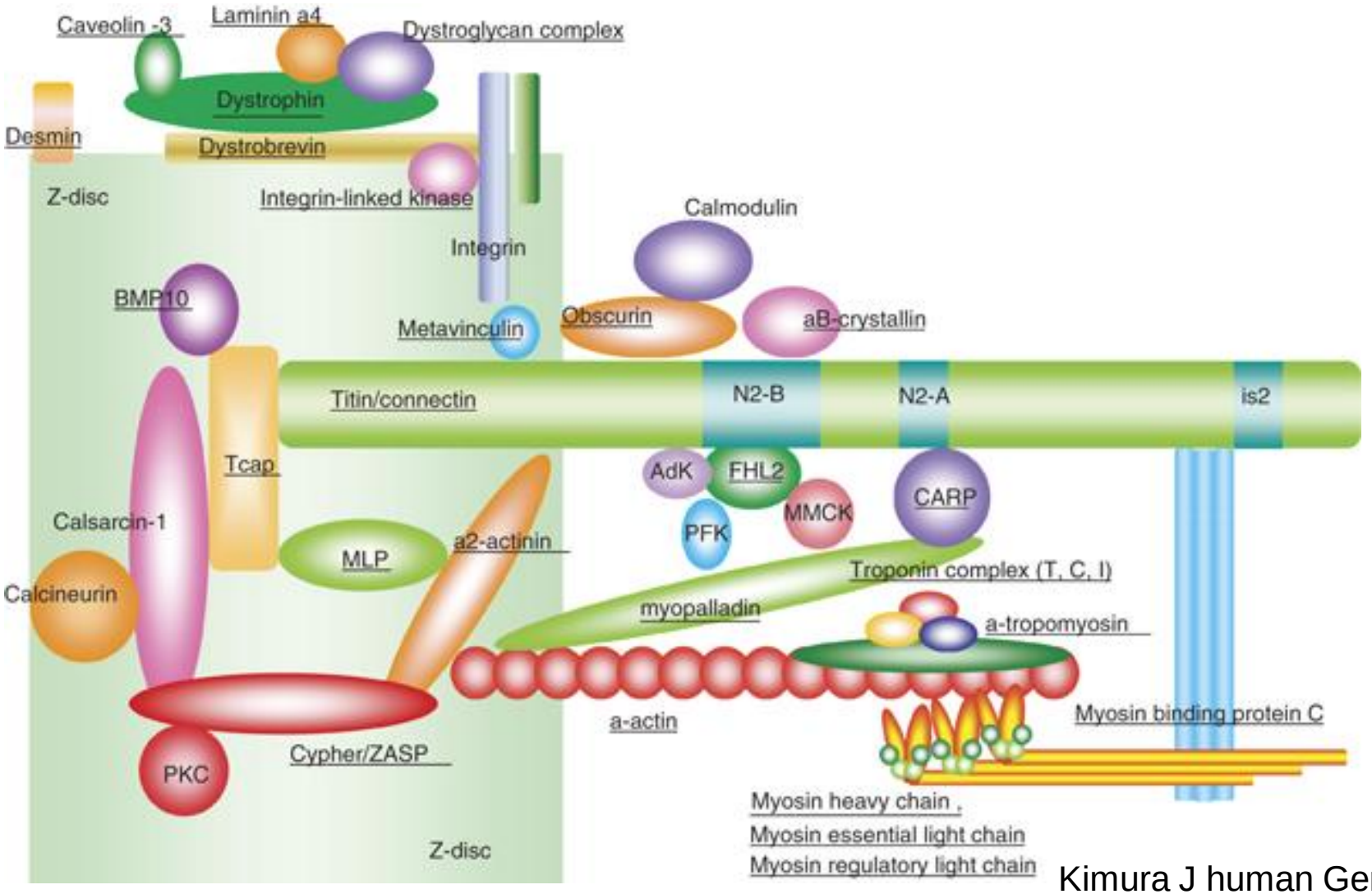


Phospholamban mutations in DCM

- Phospholamban mutations in DCM patients have been shown to be “constitutive” active (i. e. they inhibit SERCA function)

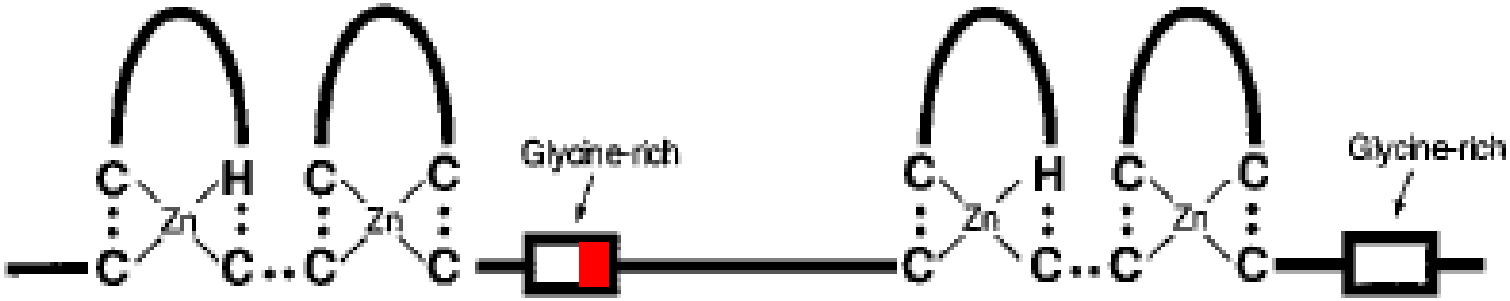

ECM
Laminin
α
β
Integrins
Extracellular
α DG
β DG
α
γ
δ
β
intracellular
Dystrophin
FAK
ILK
Z-disc:
Actin
Titin
1
2
3
Calsarcin1
Telethonin
Calcineurin
Muscle LIM Protein
ABD
R1
R2
R3
R4
α actinin
Sarcomere:
Z
I
A
M
Actin
Myosin
Myomesin
P
PLB
SERCA
SR
RyR
Emerin
Lamin A/C
Inner nuclear membrane
Outer nuclear membrane

The Z-disc / half sarcomere



Kimura J human Gen 2010

Muscle LIM Protein (MLP, CRP3 or CSRP3)



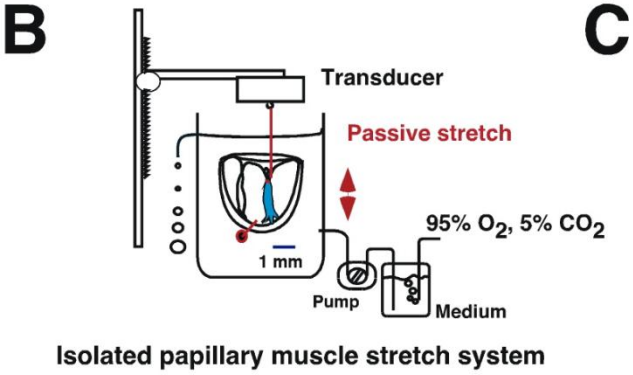
Louis et al., JBC, 1997

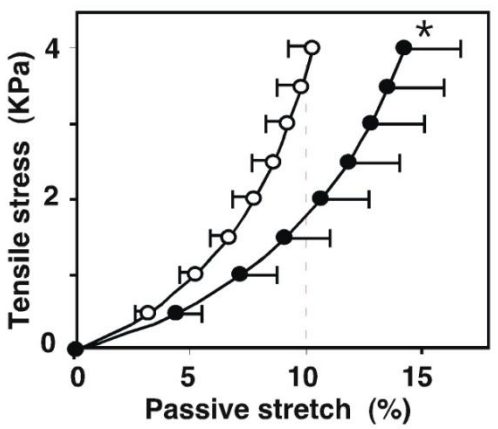
- **Member of cysteine-rich protein (CRP) family**
- **Two zinc-binding LIM domains, followed by conserved glycine-rich repeats**
- **MLP mutations cause cardiomyopathy and associated heart failure in animal models as well as in patients (Arber et al., Cell 1997; Knöll et al., Cell 2002)**
- **Nucleocytoplasmic shuttling MLP is required for adaptation to hypertrophic stimuli (Boateng et al., JMCC 2009)**
- **Underlying molecular mechanisms are not well understood**

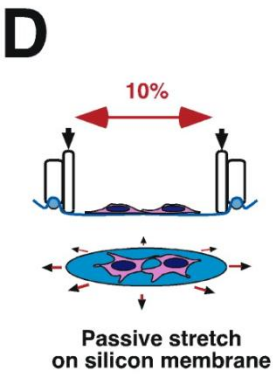
Mutations in Z-disc associated proteins

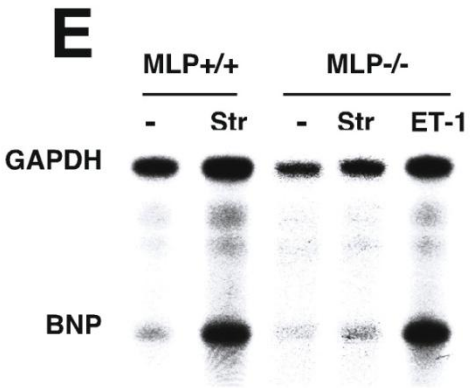
A

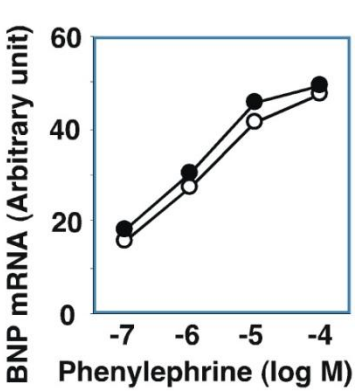
Age	2 weeks		4 weeks		8 weeks	
Genotype	MLP+/+	MLP-/-	MLP+/+	MLP-/-	MLP+/+	MLP-/-
LVEDd	2.3±0.1	2.1±0.1	3.1±0.1	3.6±0.5	3.6±0.3	5.3±0.4
LVEDs	1.1±0.1	0.9±0.1	1.7±0.8	2.4±0.8	2.5±0.3	4.4±0.3*
%FS	54±4	59±4	46±3	35±12	30±4	16±4*









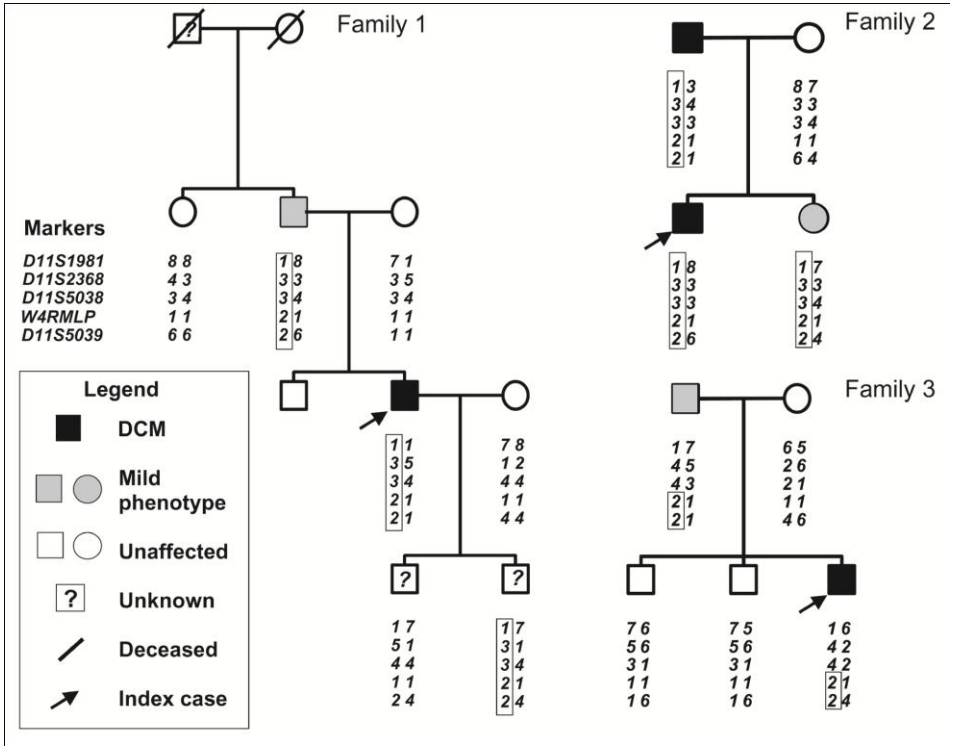


(Knöll et al., Cell 2002)

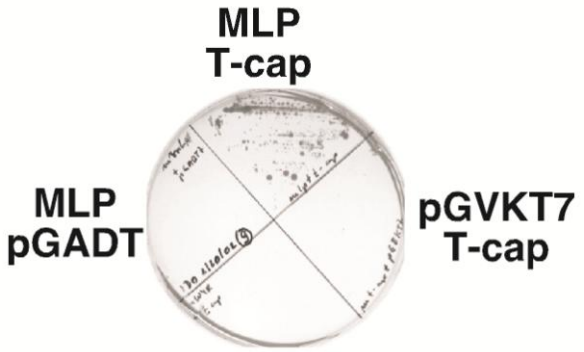
First human Z-disc – cardiomyopathy associated mutations: W4R-MLP & R87Q Telethonin (T-cap)

A

	Control	*DCM*
European population		
+/+	320	526
W4R/+	0	10*
total	320	536
Japanese population		
+/+	277	285
W4R/+	0	0
total	277	285



B



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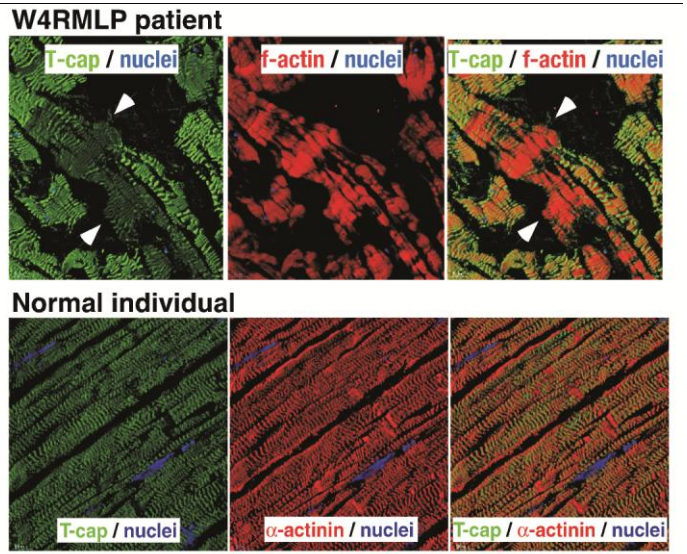
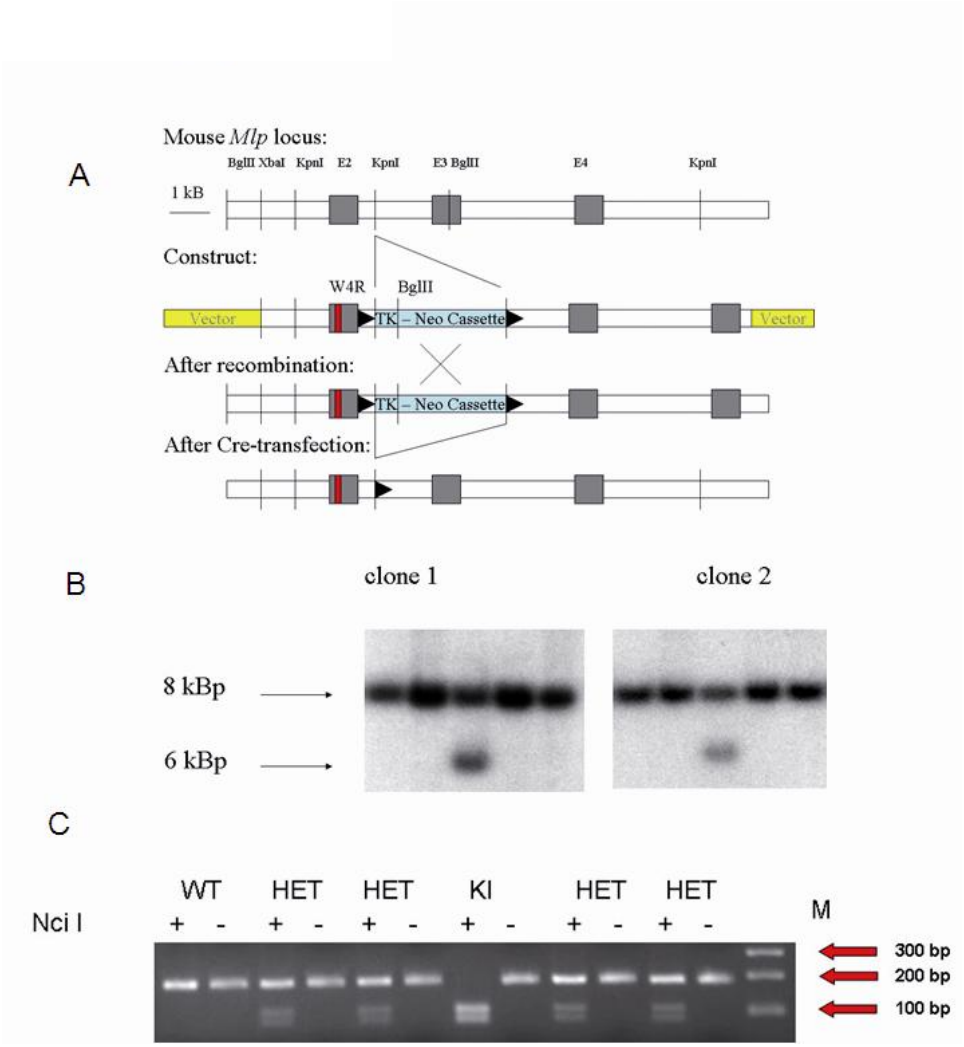


(Knöll et al., Cell 2002)

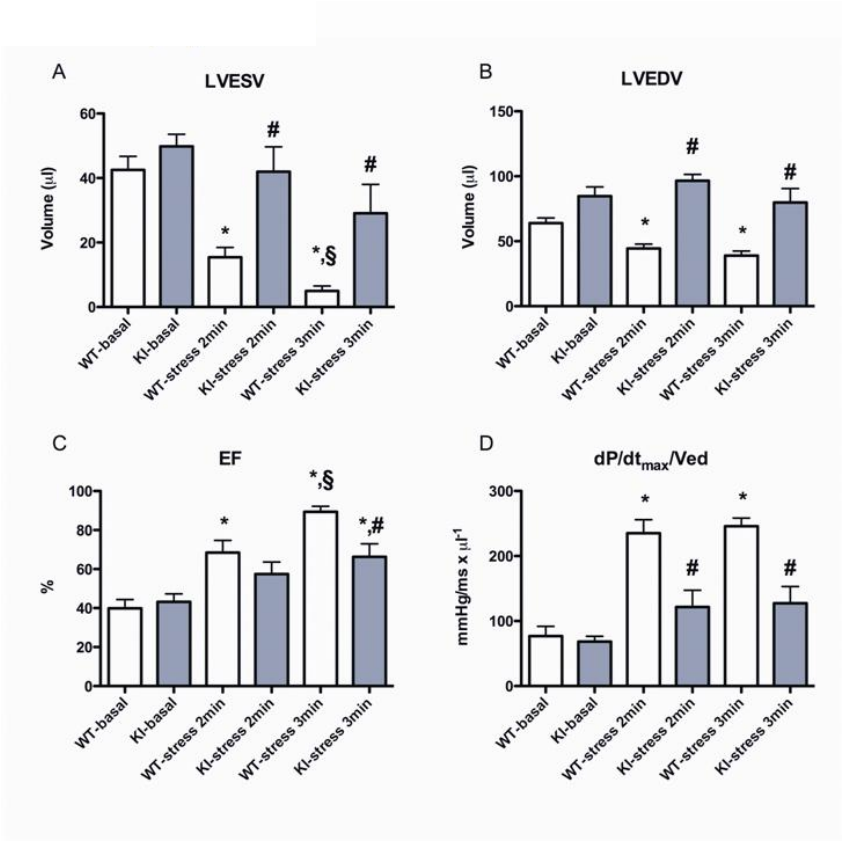
Generation of W4R-MLP knock in animals



(Knöll et al., Circulation Research 2009)

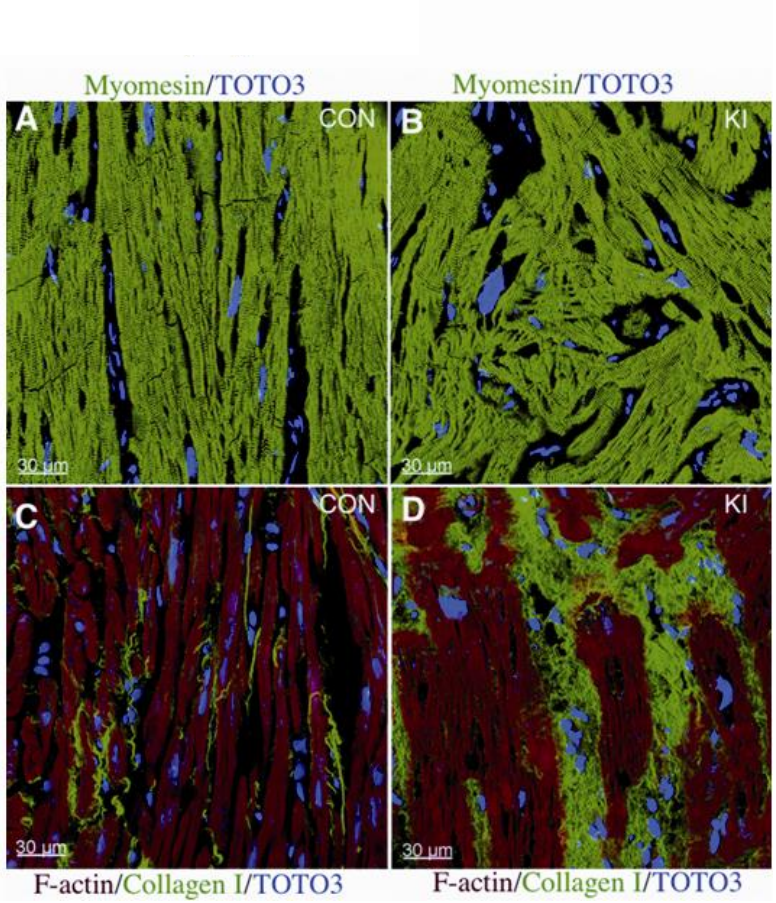
Generation and analysis of W4R-MLP knock in animals

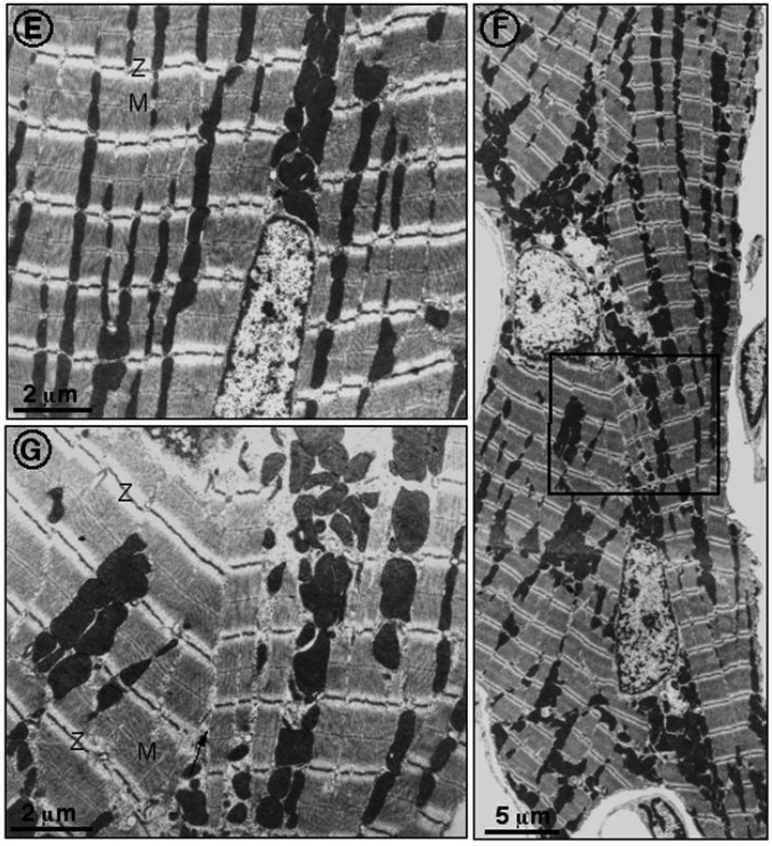
	WT Mean Value (n=18)	Heterozygous Mean Value (n=18)	Homozygous Mean Value (n=20)
SW (mm)	0.96±0.14	1.17±0.28††	1.11±0.18†
PW (mm)	0.88±0.11	0.97±0.19	1.03±0.24†
EDD (mm)	4.42±0.47	4.08±0.74	4.18±0.96
ESD (mm)	3.05±0.66	2.49±0.84†	2.65±1.19
h/r	0.43±0.08	0.55±0.19†	0.55±0.19††
FS (%)	31.7±9.3	40.4±10.8†	39.0±13.0†
HR (bpm)	521±82	569±82	547±69
Calc.LVM (mg)	181±33	188±48	196±66
BW (mg)	39.0±6.0	41.7±9.3	34.8±5.7†**
LVM/BW (mg)	4.65±0.59	4.56±0.83	5.71±2.07†*



(Knöll et al., Circulation Research 2009)

Generation and analysis of W4R-MLP knock in animals

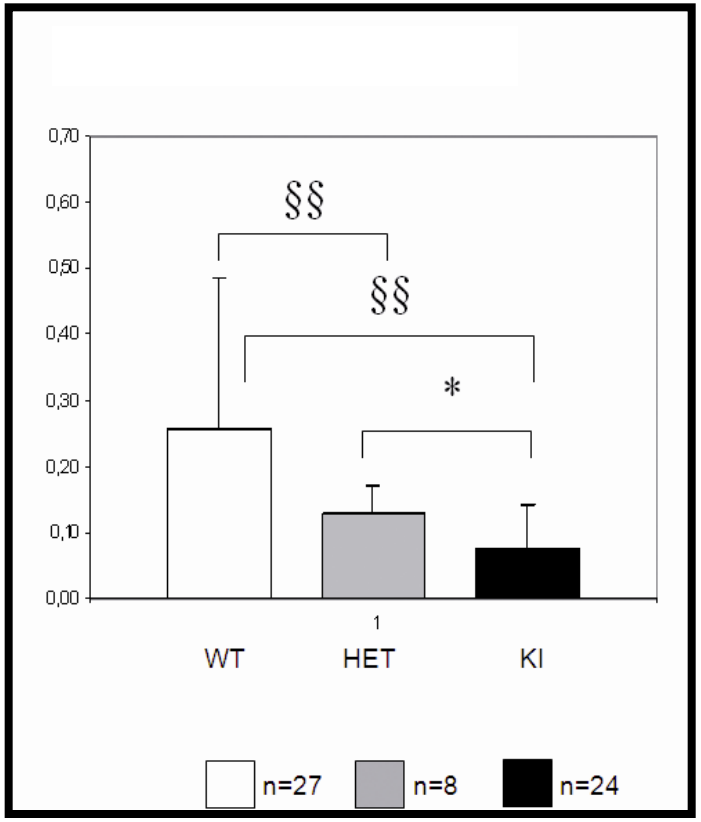




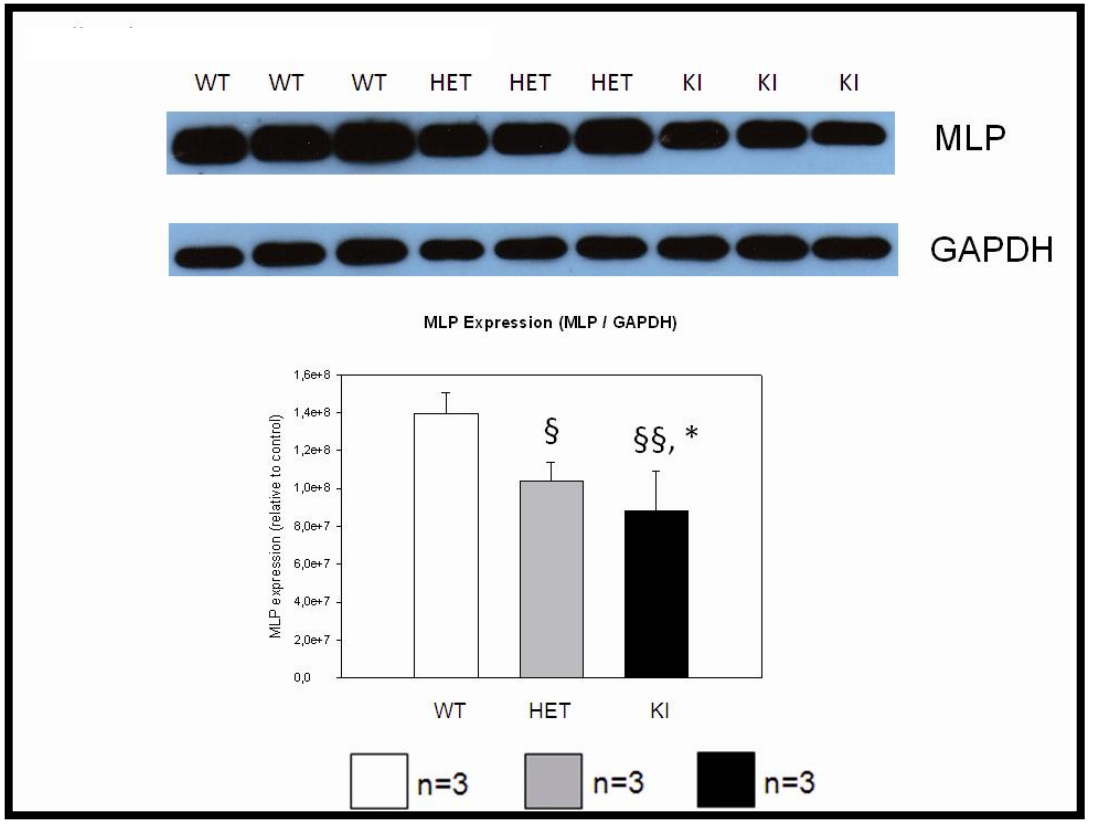
(Knöll et al., Circulation Research 2009)

Generation and analysis of W4R-MLP knock in animals

MLP mRNA:

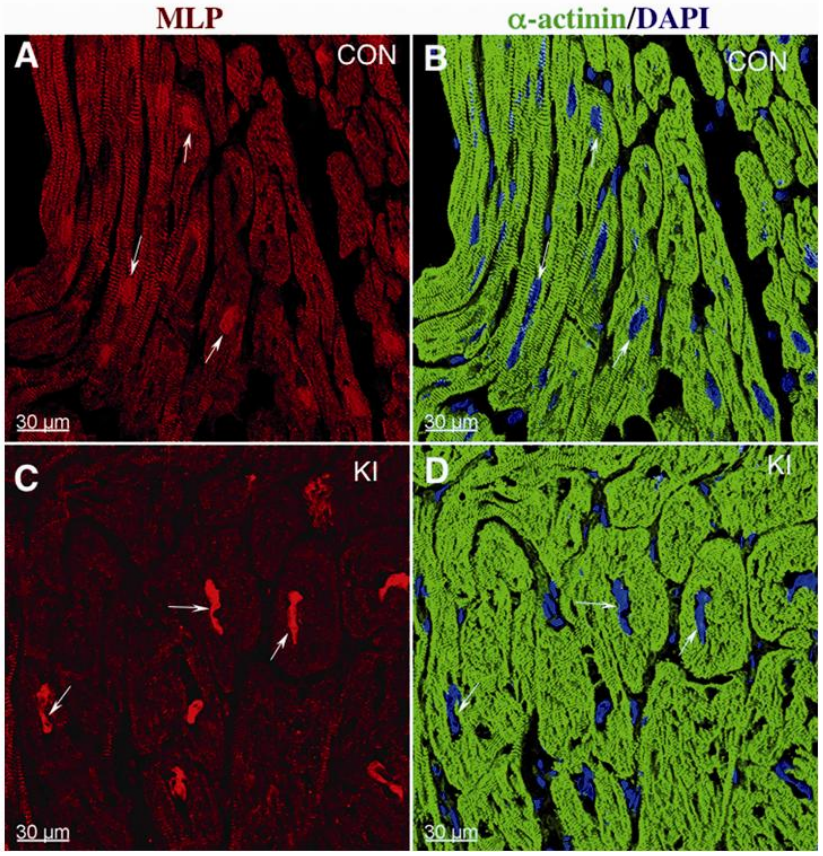


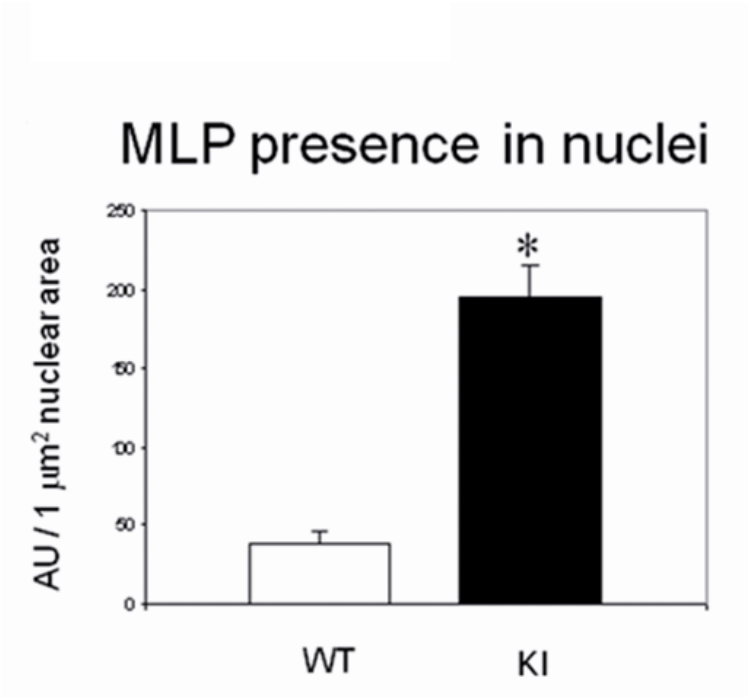
MLP protein:



(Knöll et al., Circulation Research 2009)

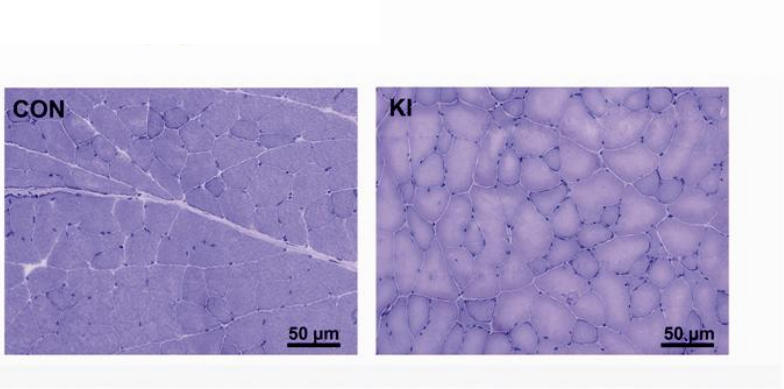
Generation and analysis of W4R-MLP knock in animals

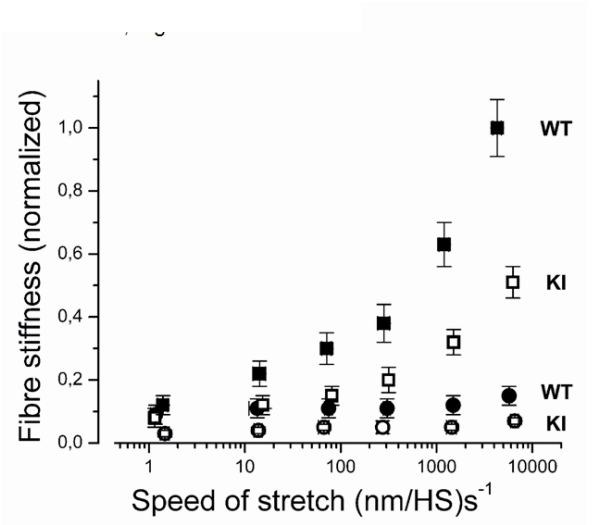




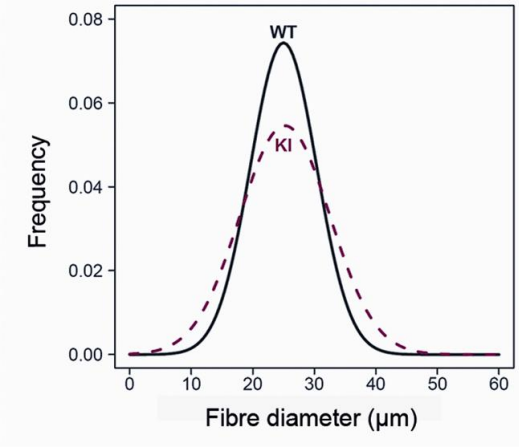
(Knöll et al., Circulation Research 2009)

Skeletal Muscle Phenotype

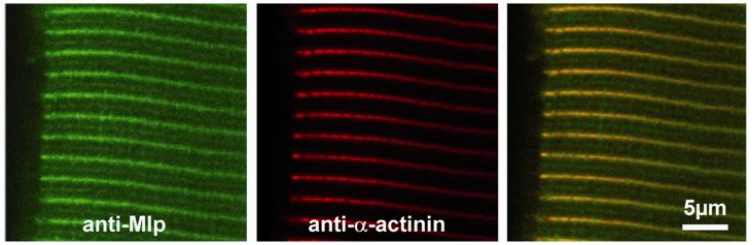




Knöll et al., Fig. 6 B

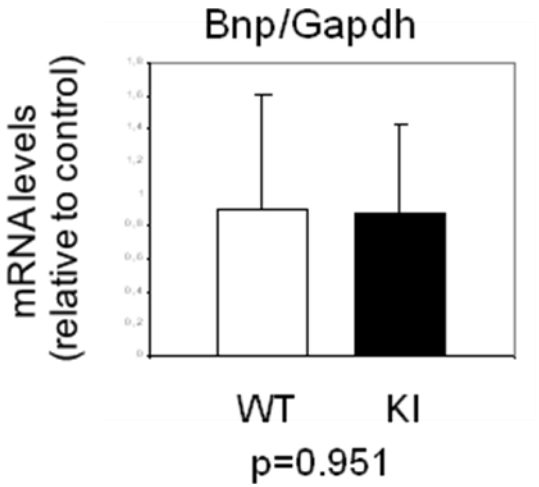


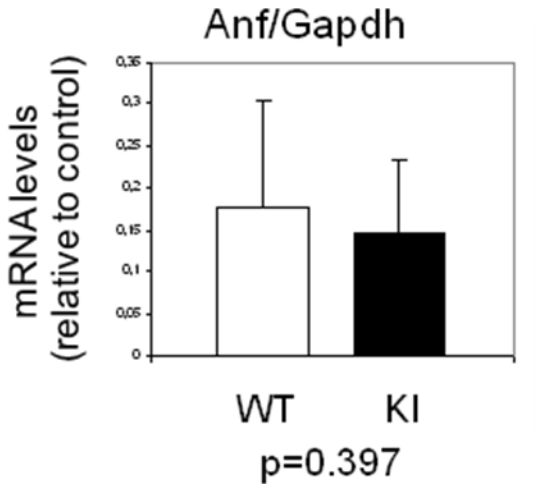
Knöll et al., Fig. 6 D

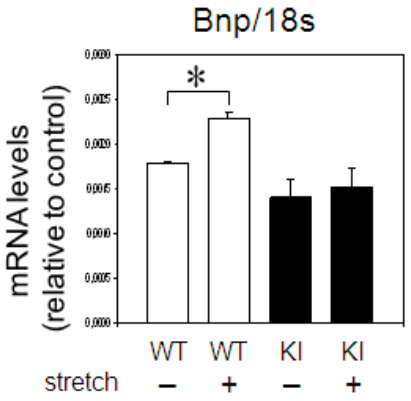


(Knöll et al., Circulation Research 2009)

Cell Stretch Experiments

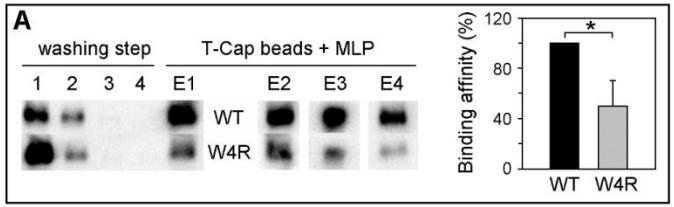


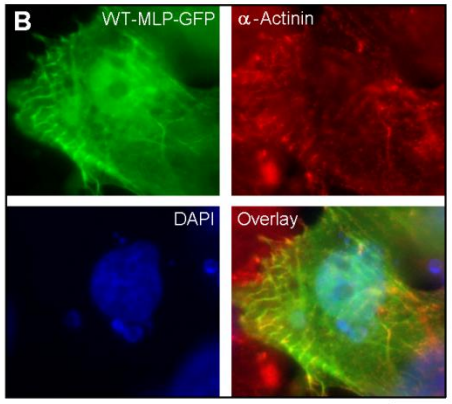


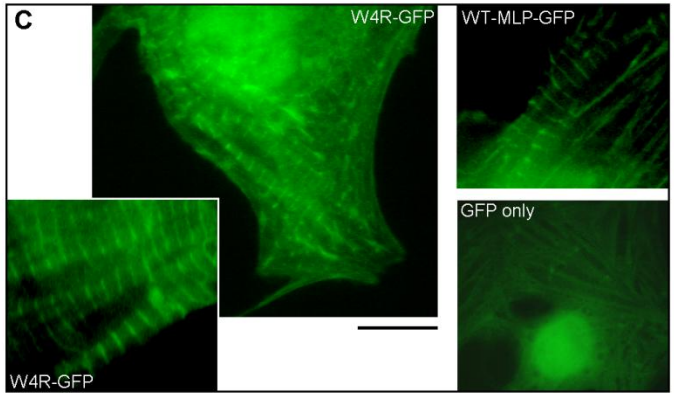


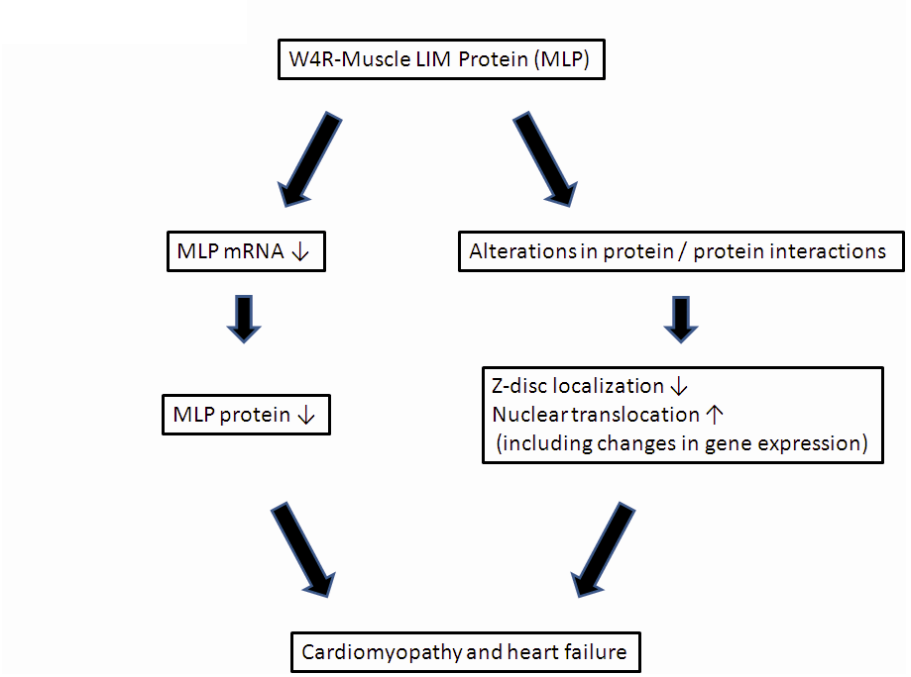
(Knöll et al., Circulation Research 2009)

Localization of MLP and W4R-MLP







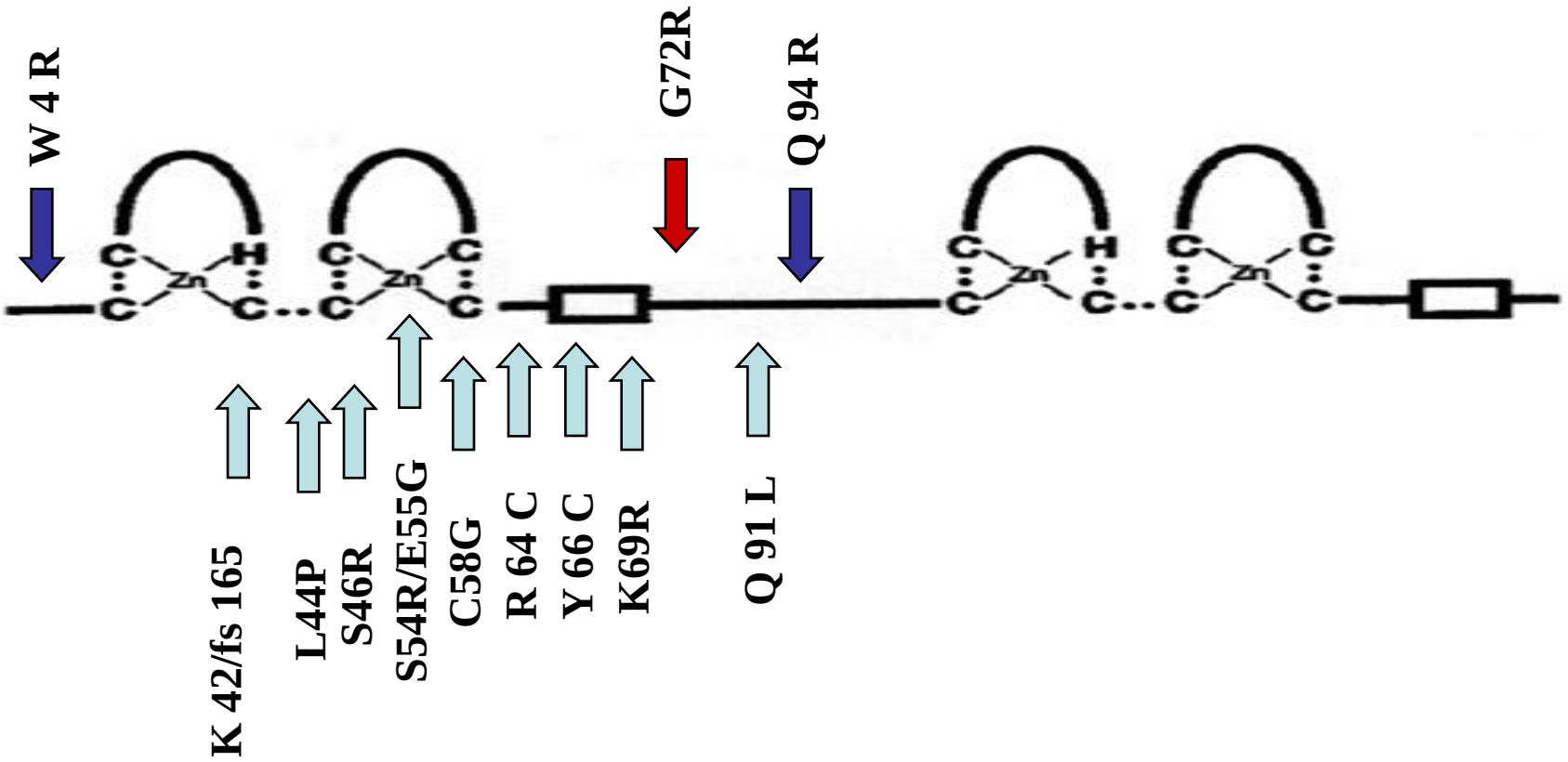


(Knöll et al., Circulation Research 2009)

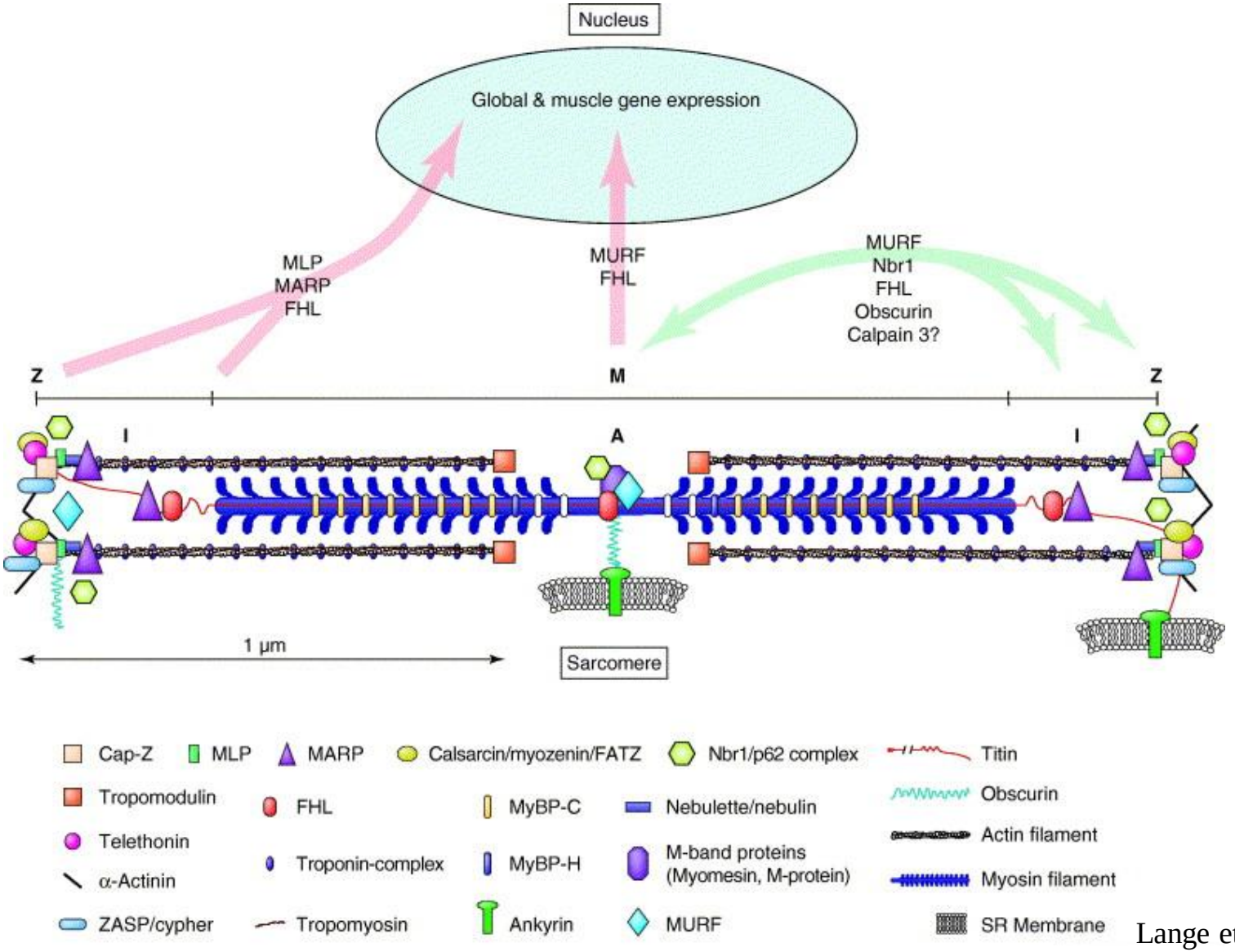
W4R-MLP

- W4R-MLP is present in different caucasian populations (up to 1%) and as such only comparable to a MYBPC disease causing mutation present in southeast asia at a frequency of about 4% (Dhandapany Nat Gen 2009)
- W4R-MLP causes a cardiomyopathy and heart failure phenotype as well as a mild skeletal muscle phenotype
- Because of it‘s high frequency, W4R-MLP is an important human disease gene

MLP Mutations:
Localization and Phenotype

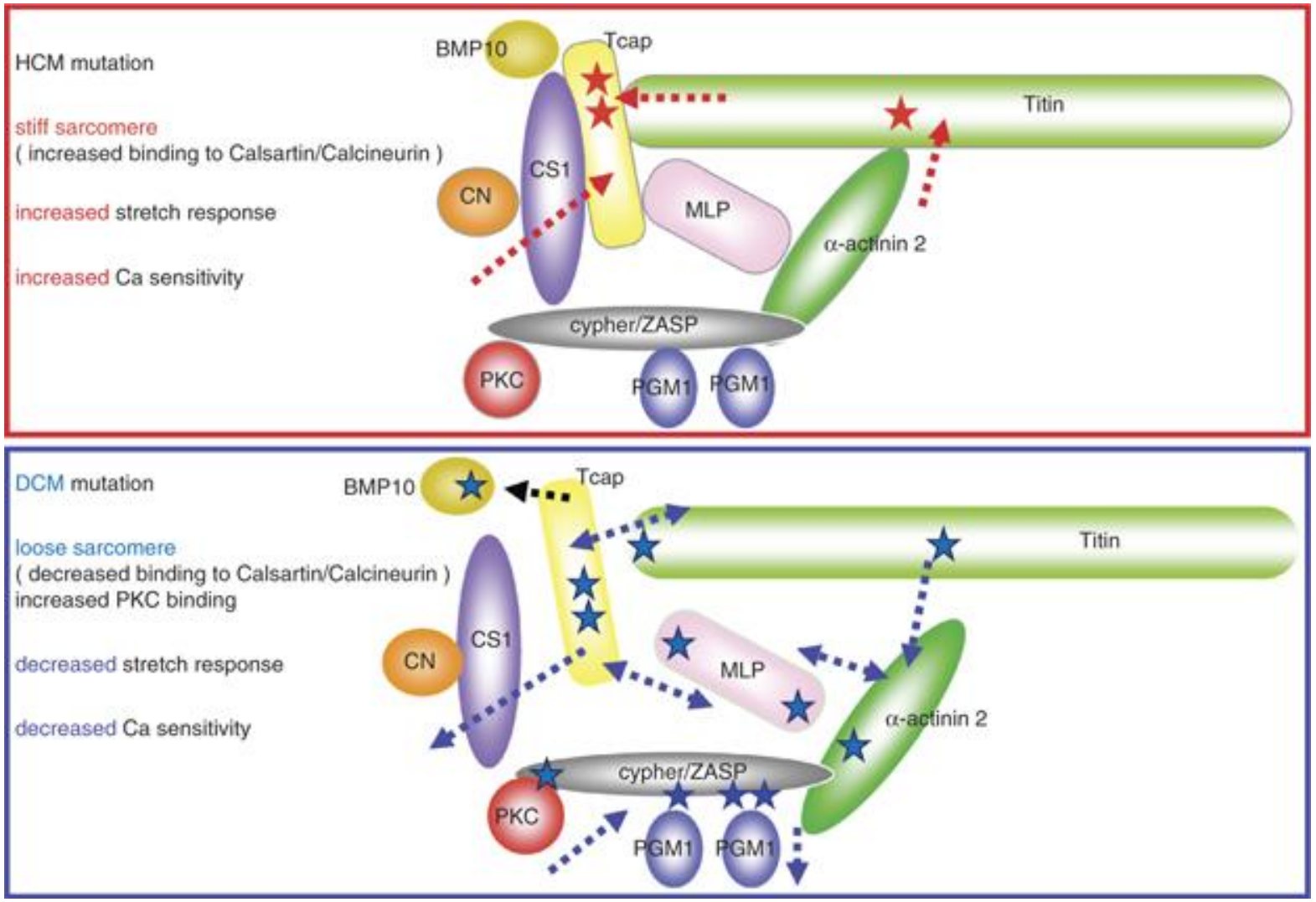


Z-disc/sarcomeric - nuclear exchange



Lange et al. 2005

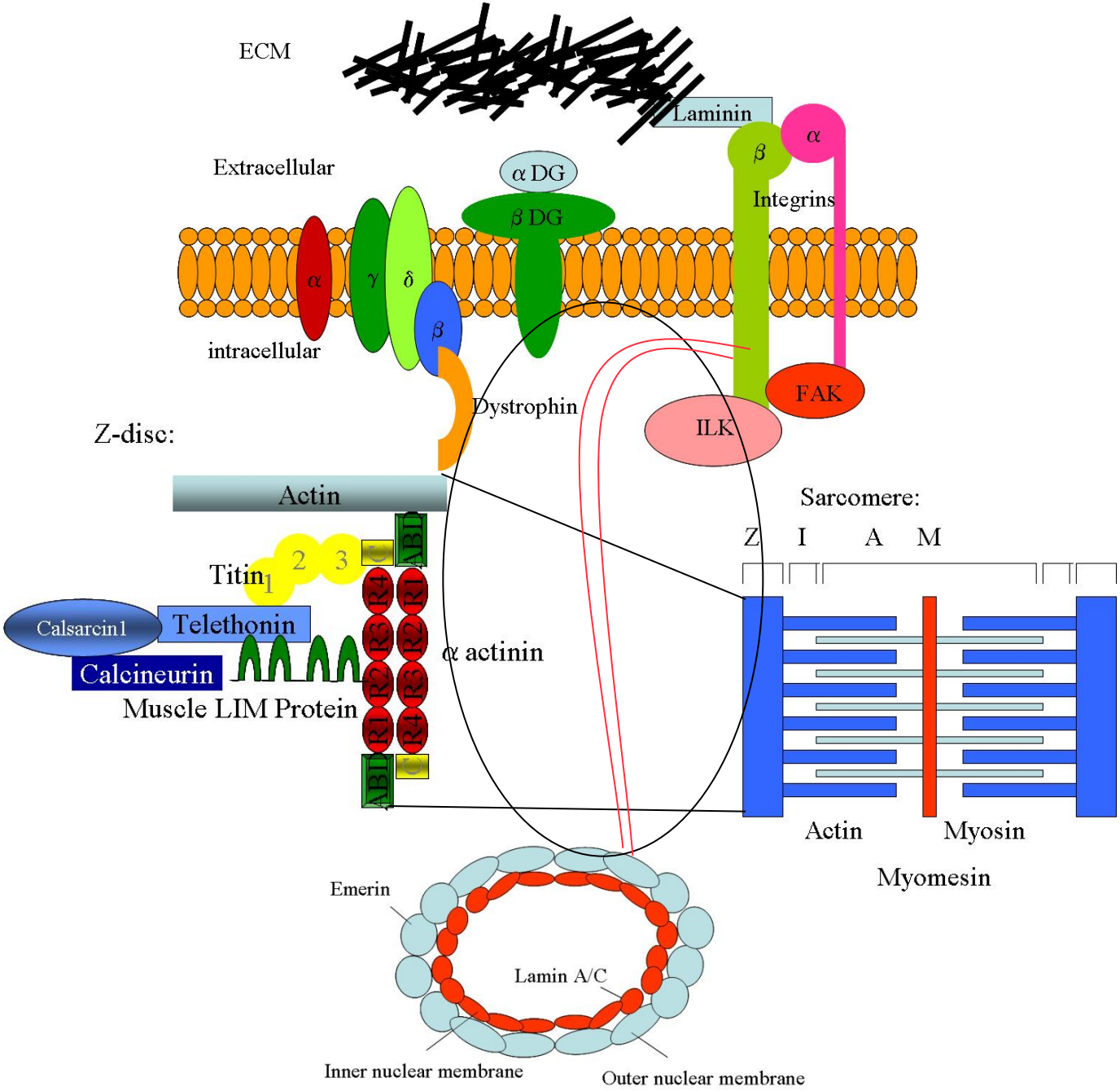
Z-disc and cardiomyopathy



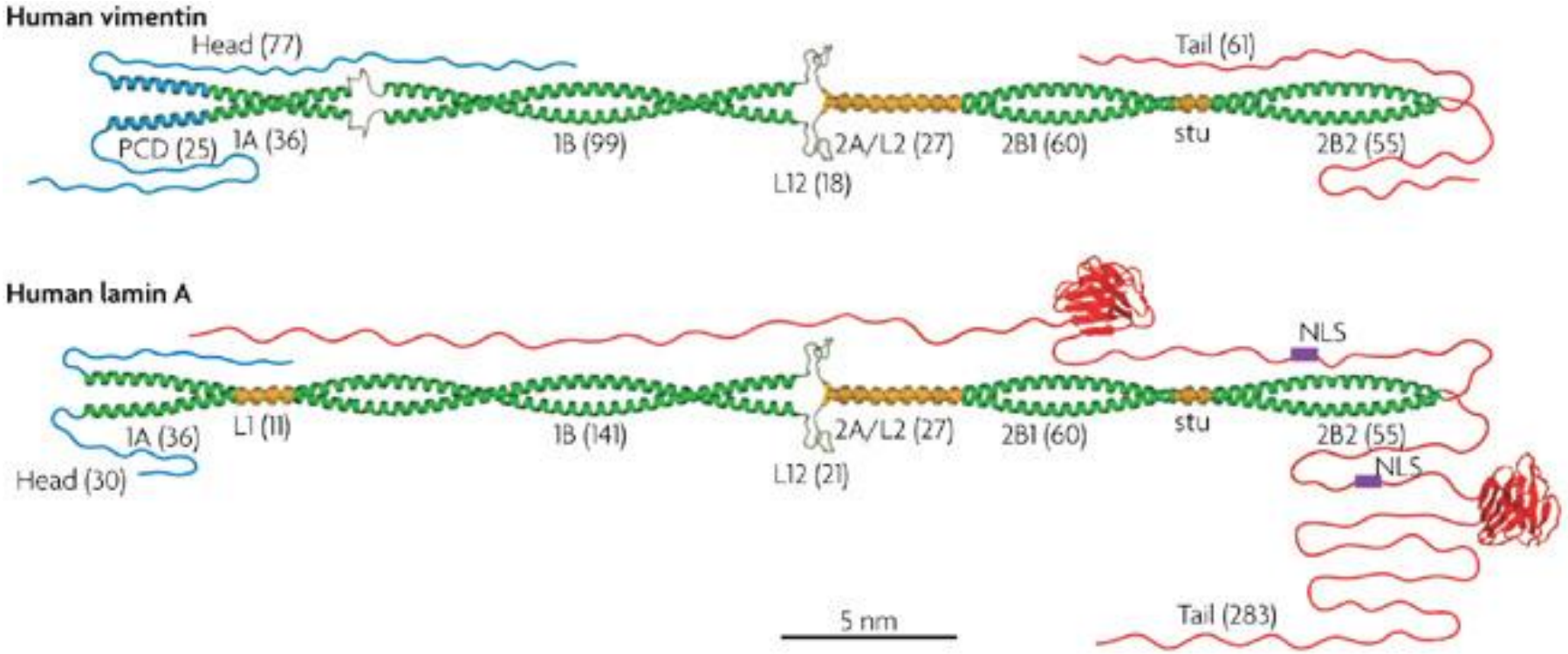
Kimura J human Gen 2010

Z-disc protein mutations

- May cause cardiomyopathy by affecting cardiac mechanosensation
- May also cause cardiomyopathy by changing interactions with other Z-disc components (i. e. an increase in affinity to interacting partners may lead to an increased stiffness of the Z-disc and hence an increase in calcium sensitivity or vice versa)

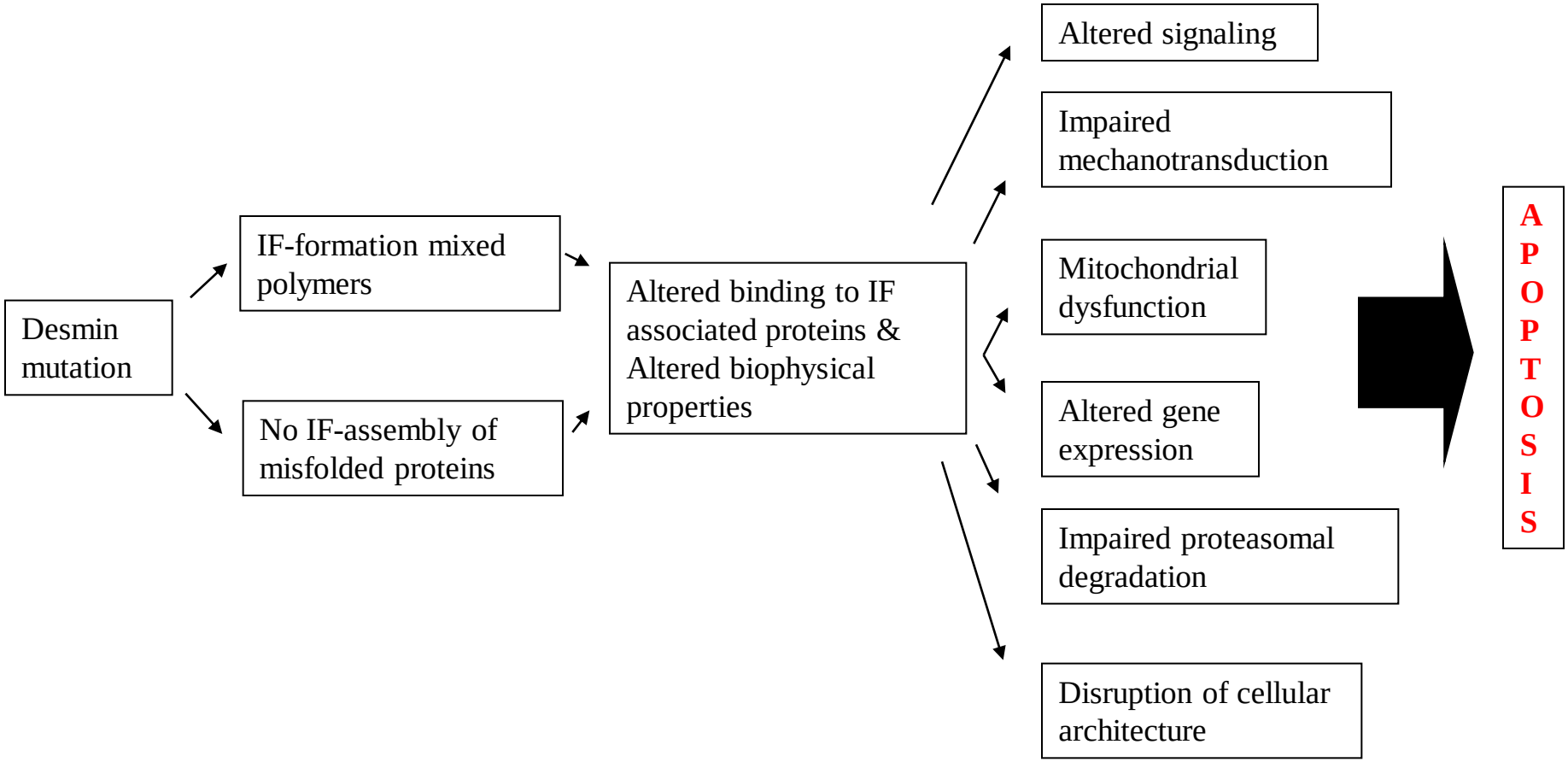

ECM
Laminin
α
β
Integrins
Extracellular
α DG
β DG
α
γ
δ
β
intracellular
Dystrophin
FAK
ILK
Z-disc:
Actin
Sarcomere:
Z I A M
Titin
1
2
3
ABD
R4
R3
R2
R1
Calsarcin1
Telethonin
Calcineurin
Muscle LIM Protein
α actinin
Actin
Myosin
Myomesin
Emerin
Lamin A/C
Inner nuclear membrane
Outer nuclear membrane

Intermediate Filaments

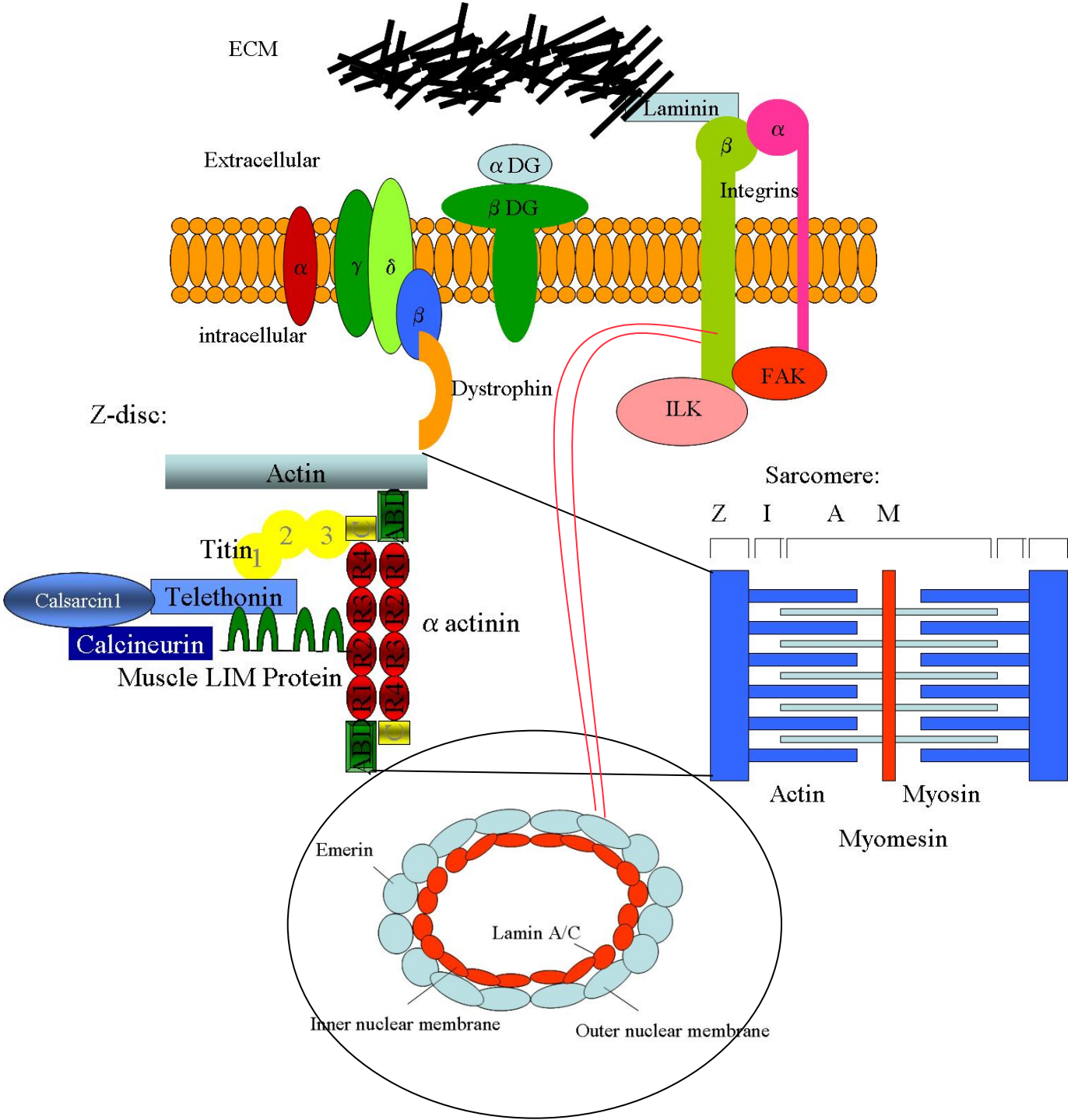


(Herrmann et al, 2007)

Intermediate Filaments – Potential Pathomechanism



(Aebi et al, 2007)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α actinin
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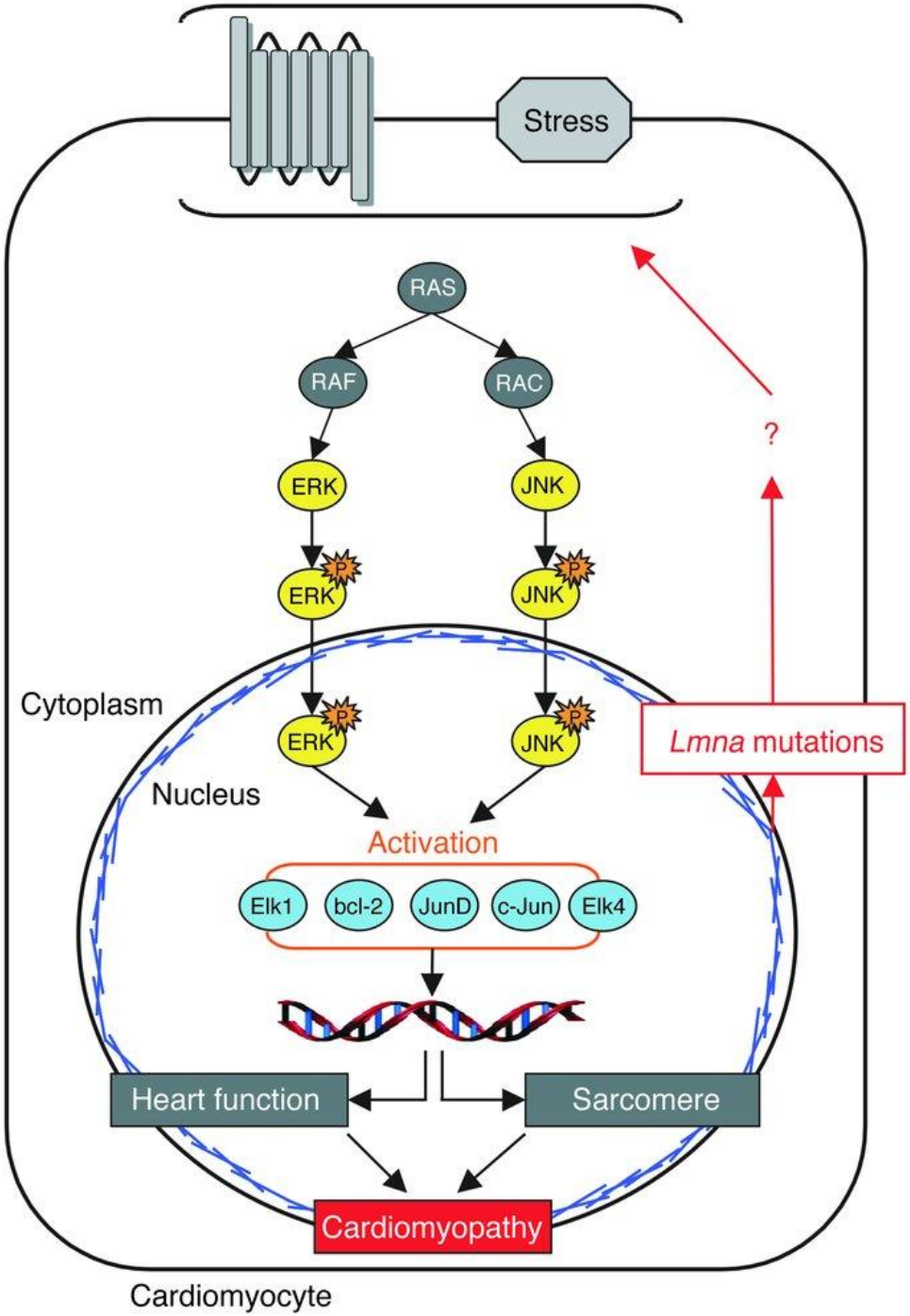
I
A
M
Actin
Myosin
Myomesin
Emerin
Lamin A/C
Inner nuclear membrane
Outer nuclear membrane

Nuclear Membrane Proteins

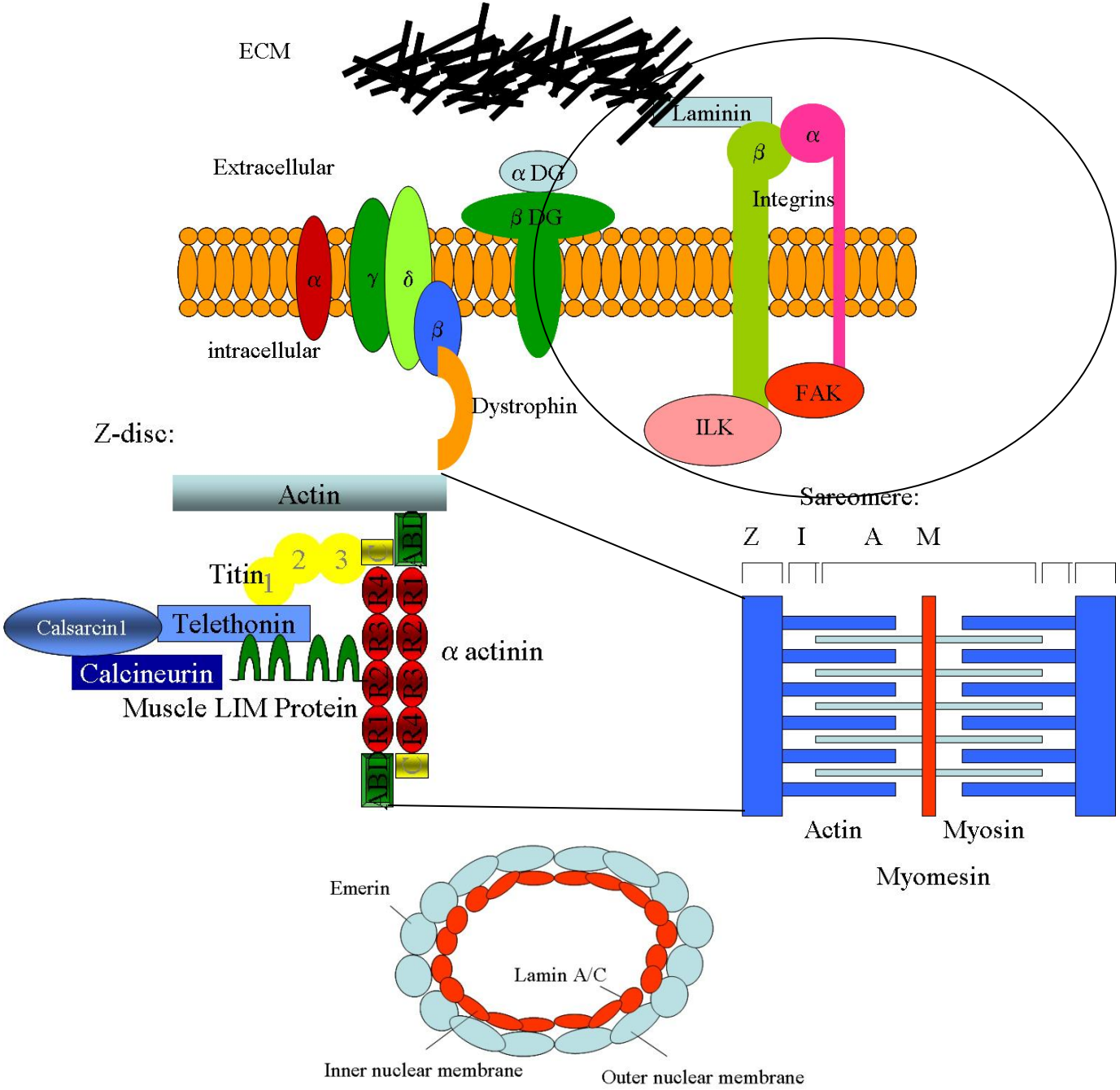
- Lamin A/C (LMNA) and Emerin (EMD)
- Disease causing mechanisms remain unclear, but:
- 1. defects in stretch response
- 2. H222P-LMNA mutation might activate the MAPKinase pathway - suggesting changes in signal transduction cascades are involved in the pathogenesis of DCM



Model of how abnormalities of A-type lamins in the nuclear lamina may lead to cardiomyopathy.

Abnormalities of A-type lamins in the nuclear lamina activate MAPK cascades, possibly via heterotrimeric G-protein receptors or by inducing stress responses by unknown mechanisms (?). This leads to activation of G-proteins (RAS and RAC), protein kinase (RAF), and subsequent enhanced phosphorylation of ERK and JNK1/2, resulting in nuclear translocation. In the nucleus, pERK1/2 and pJNK activate transcription factors such as Elk1, bcl-2, JunD, c-Jun, and Elk4, leading to increased synthesis of these proteins. Increased amounts and activities of transcription factors activated by pJNK and pERK1/2 alter expression of other genes, some encoding components of muscle fibers and sarcomeres. Aberrant expression of these proteins leads to development of cardiomyopathy.

Muchir et al., JCI 2007


ECM
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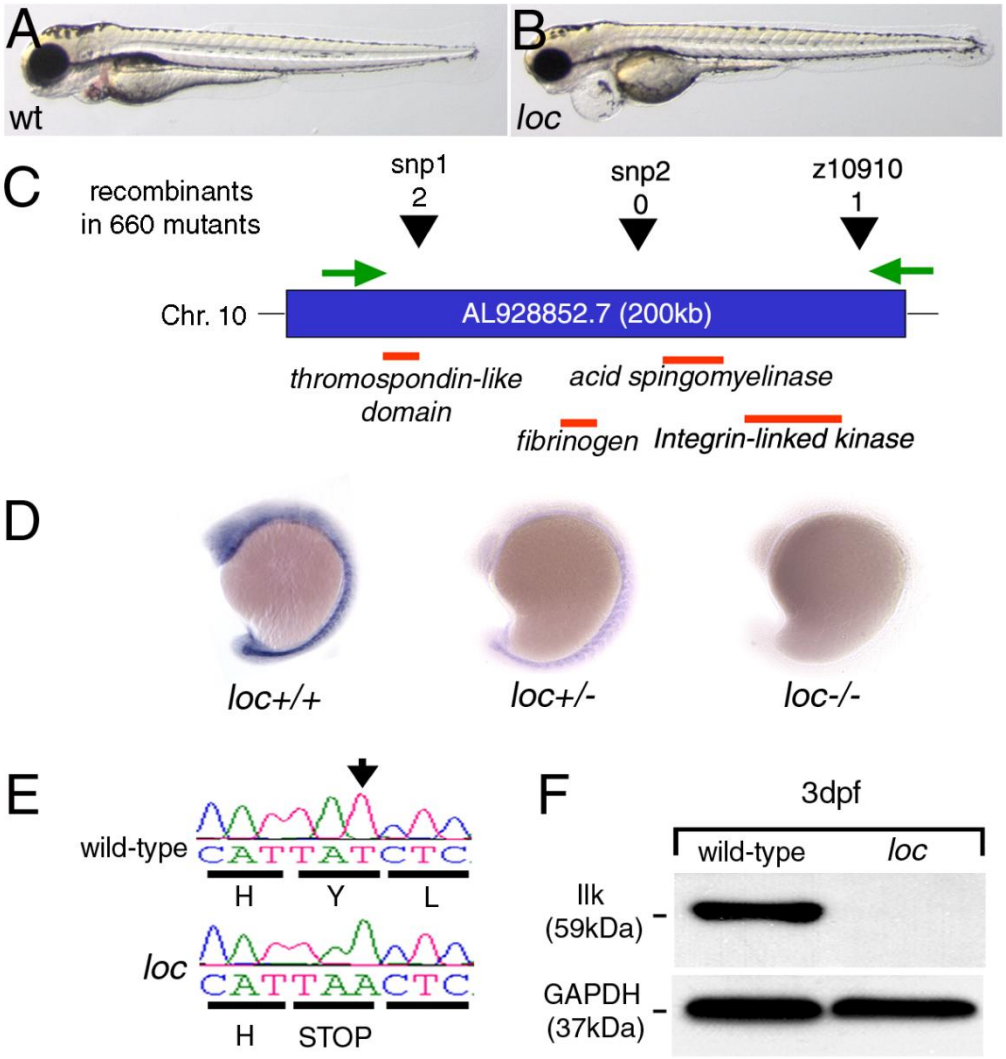
Muscle LIM Protein
α actinin
Sarcomere:
Z
I
A
M
Actin
Myosin
Myomesin
Emerin
Lamin A/C
Inner nuclear membrane
Outer nuclear membrane

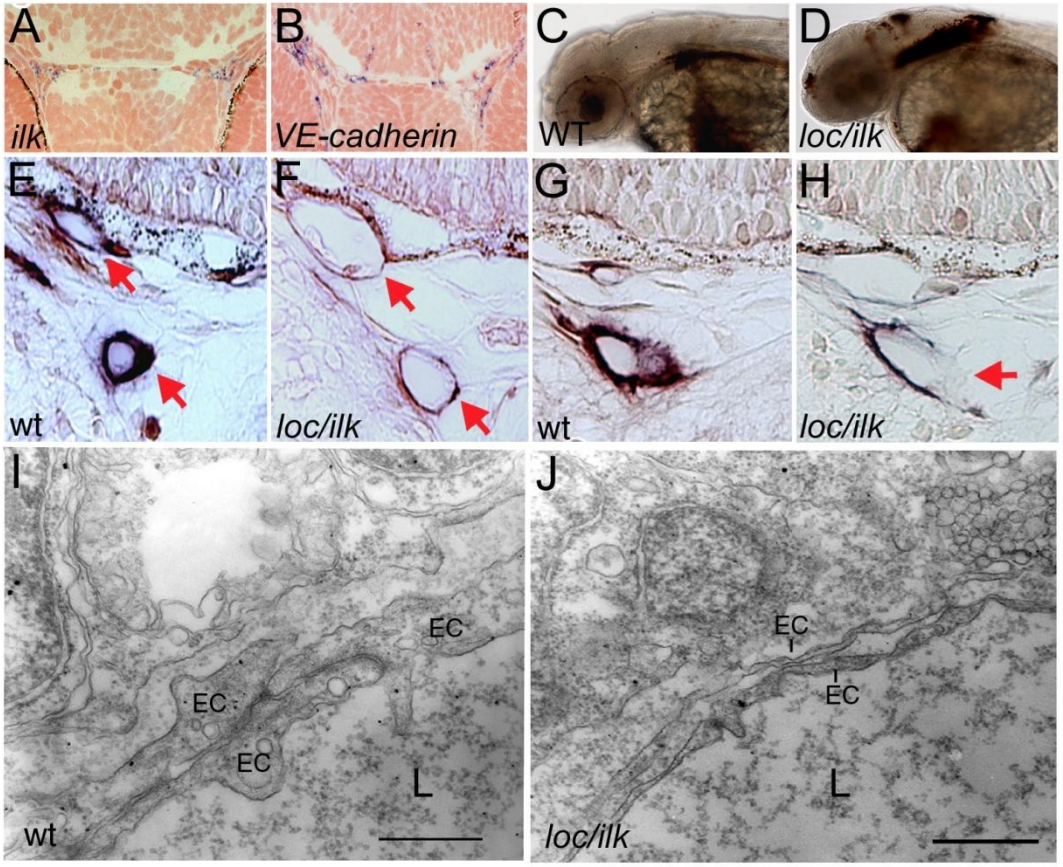
Postional cloning of the lost contact gene (loc/Y319X-ILK)



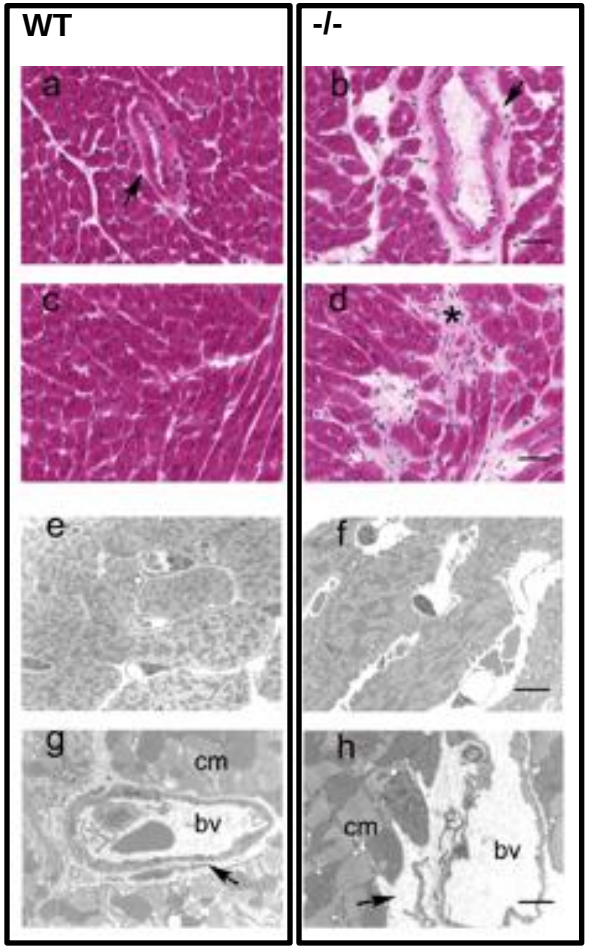
(Knöll...Bakkers, Circulation 2007)

Similarities between *loc* zebra-fish & lama4 -/- mouse model

loc (ilk -/-) zebrafish:

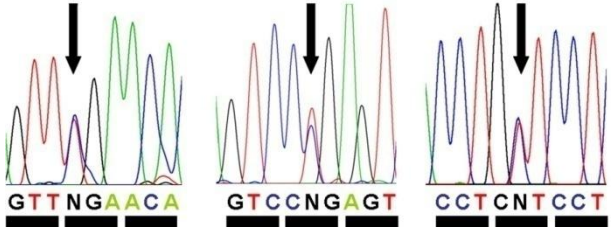


lama4 -/- mouse:



(Knöll et al., Circulation 2007)

Human ILK and LAMA 4 mutations



Sequence comparison of different lama 4 proteins in the area of P943

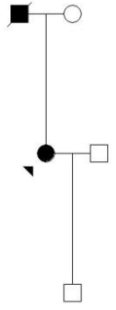
aa939	F	L	T	V	P	S	L	S	S	homo sapiens
aa941	F	L	T	V	P	S	L	S	S	mus musculus
aa929	F	L	T	V	P	S	L	S	S	canis familiaris
aa1064	F	L	T	I	P	S	L	S	S	gallus gallus

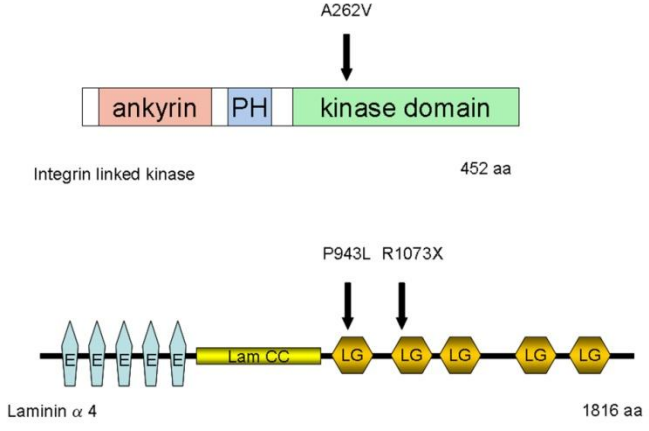
Sequence comparison of different lama 4 proteins in the area of R1703

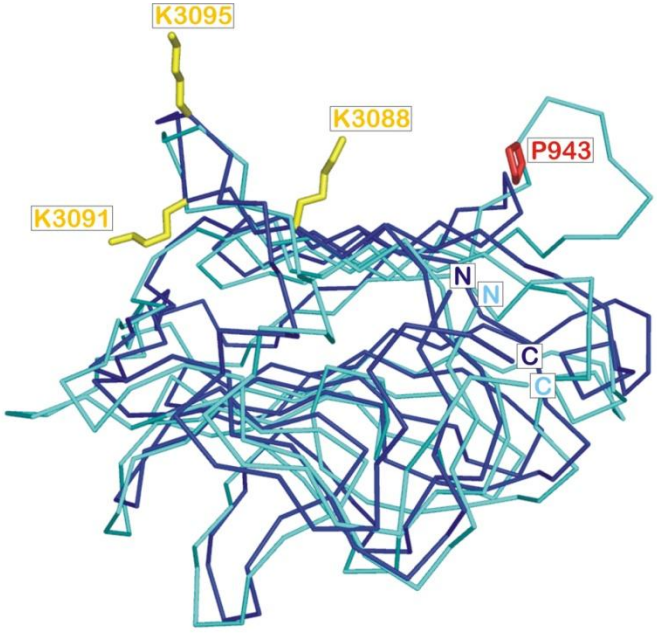
aa 1069	D	I	E	V	R	T	P	A	D	homo sapiens
aa 1071	D	I	E	I	R	T	P	A	D	mus musculus
aa 1059	D	I	E	V	R	T	P	A	D	canis familiaris
aa 1194	D	I	E	V	R	T	P	S	D	gallus gallus

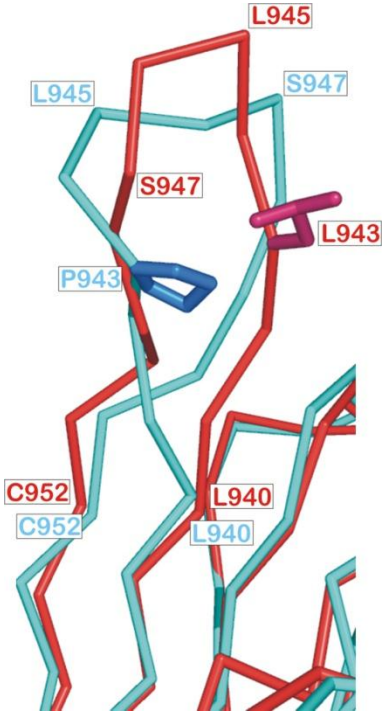
Sequence comparison of different ILK proteins in the area of A262

aa258	Q	S	P	P	A	P	H	P	T	homo sapiens
aa258	Q	S	P	P	A	P	H	P	T	mus musculus
aa258	Q	S	P	P	A	P	H	P	T	gallus gallus
aa258	Q	S	P	P	A	P	H	P	T	danio rerio



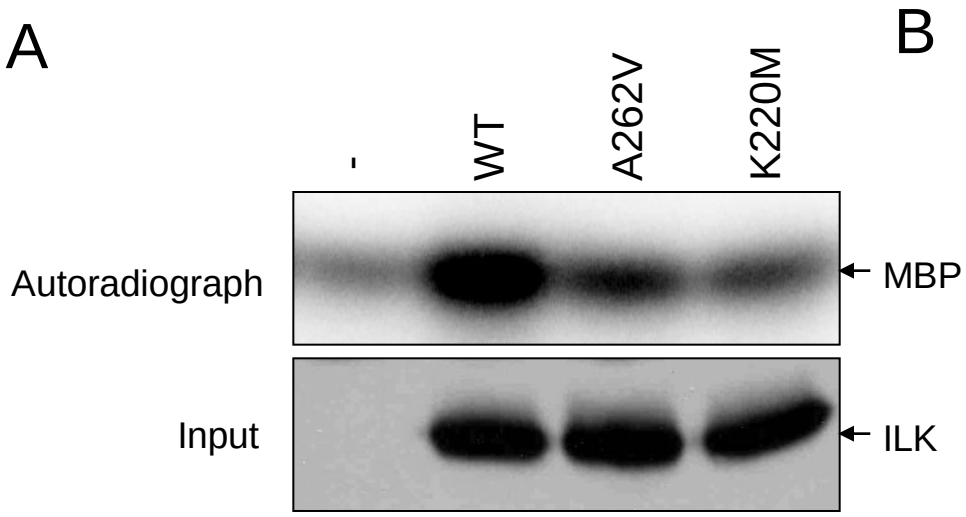


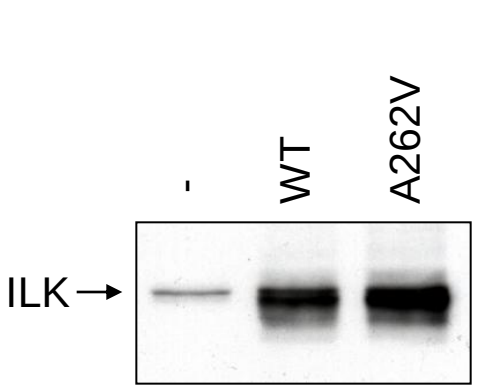


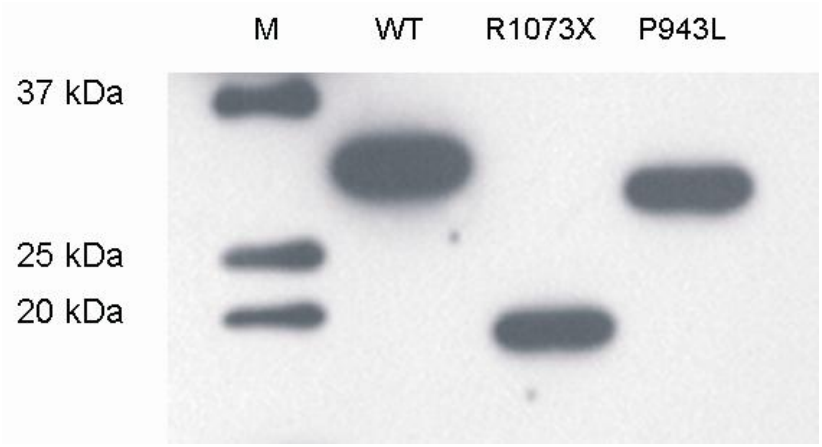


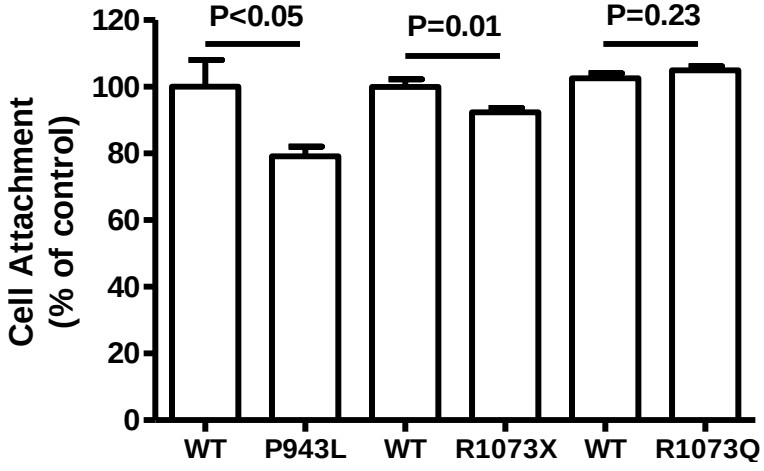
(Knöll et al., Circulation 2007)

Functional characterization of human ILK and laminin α4 mutations

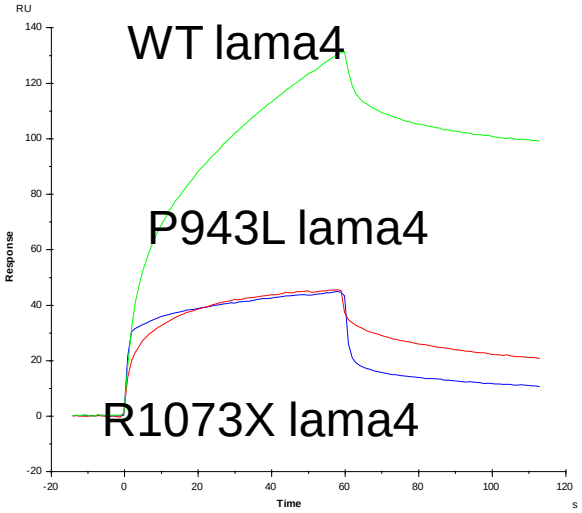


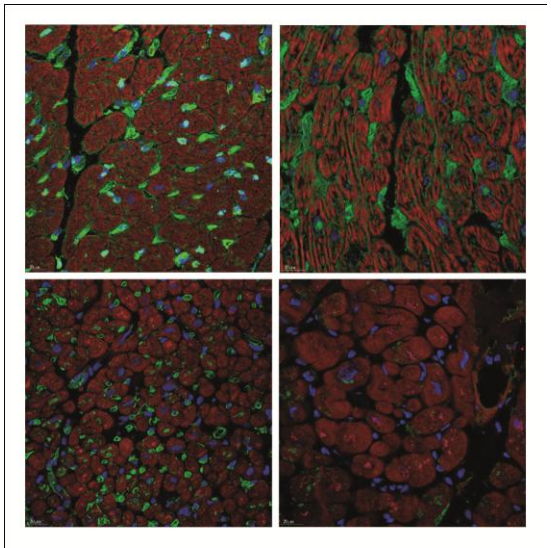


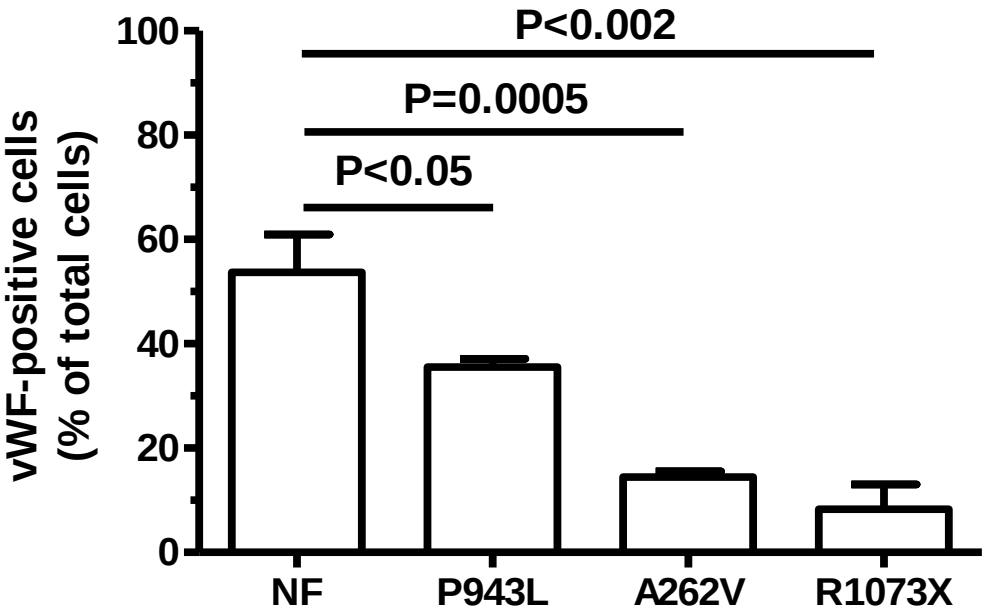




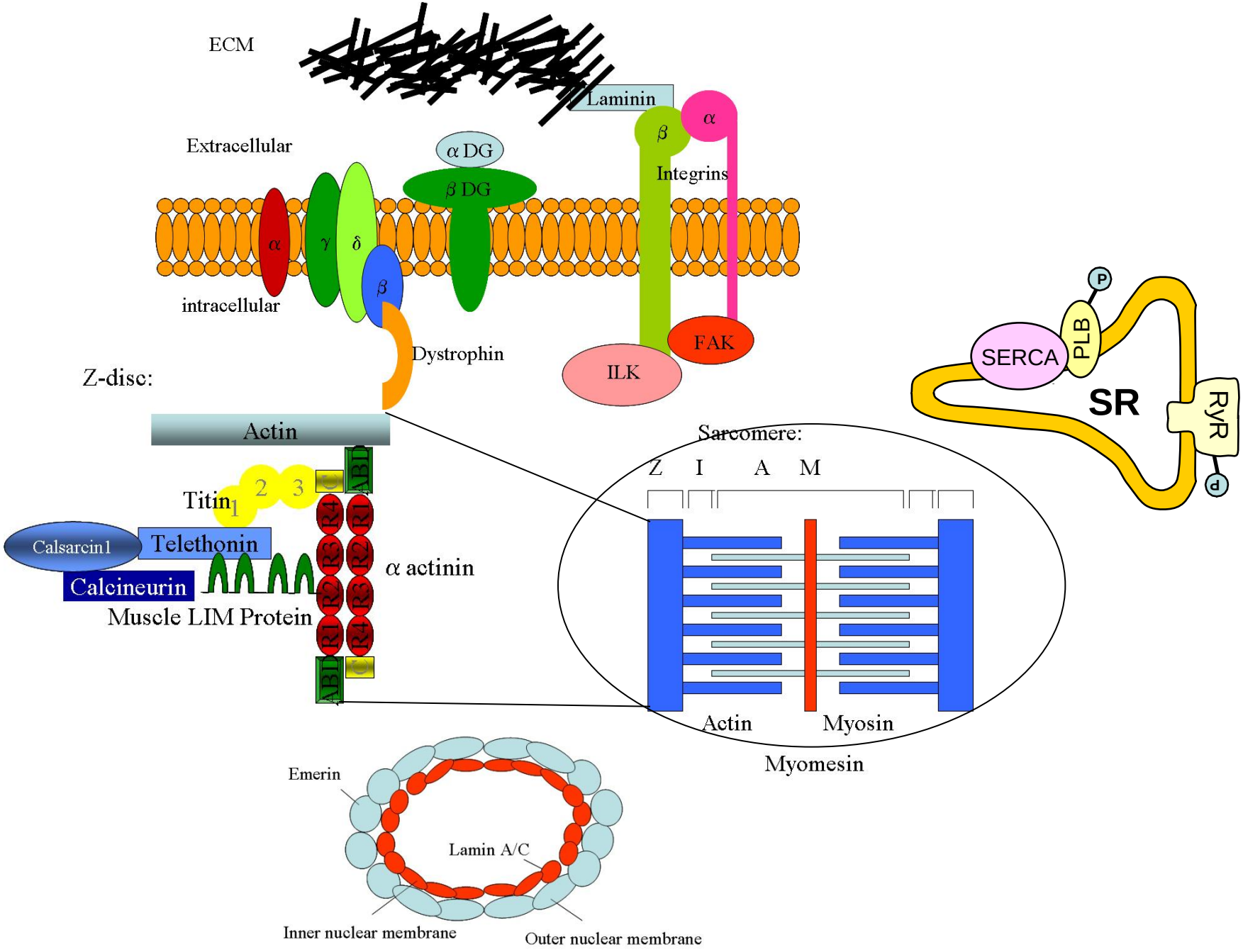
ILK & LAMA4 mutations affect endothelial cells







(Knöll et al., Circulation 2007)


ECM
Laminin
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Z-disc:
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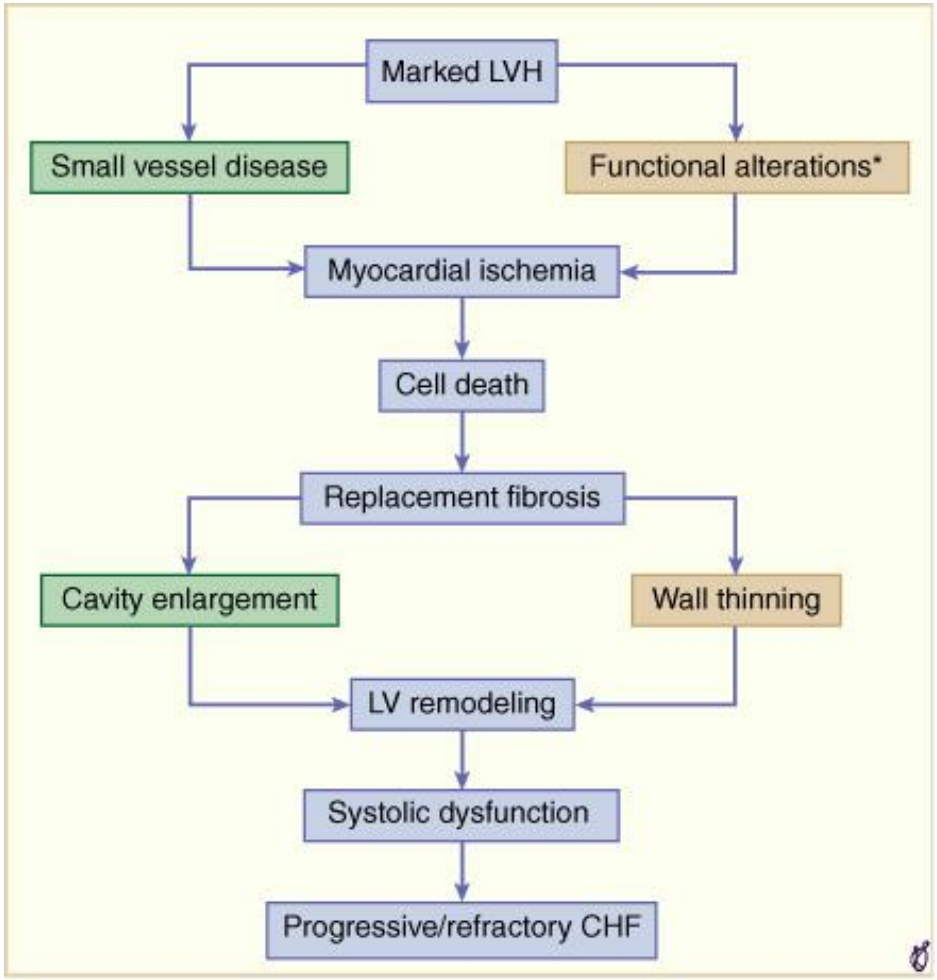
Z
I
A
M
Actin
Myosin
Myomesin
P
PLB
SERCA
SR
RyR
Emerin
Lamin A/C
Inner nuclear membrane
Outer nuclear membrane

Mutations in sarcomeric components & possible transition to DCM



Genes:
MybPC
β-Myosin-Heavy Chain
Cardiac Troponin T
Cardiac Troponin C
Cardiac Troponin I
α-Tropomyosin

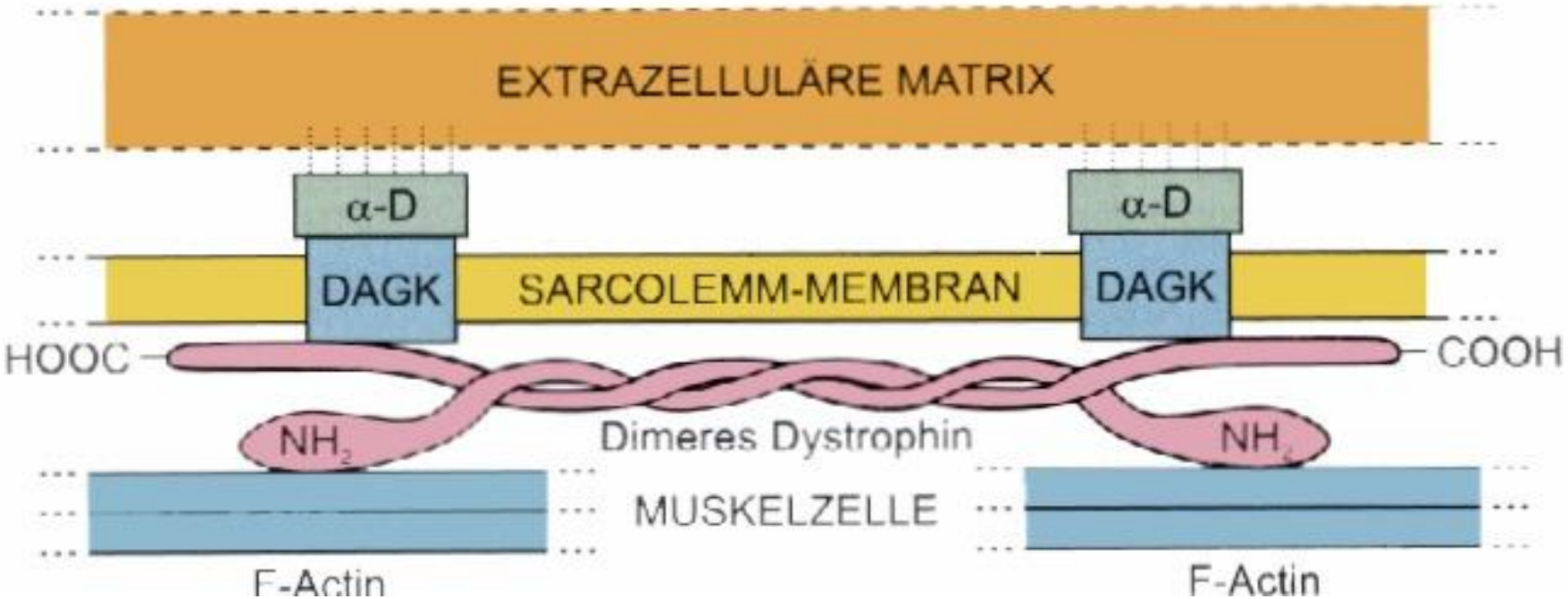
Types of mutation:
Heterozygous versus
Homozygous
Compound heterozygous
Double heterozygous

(Maron BJ, Spirito P;. Am J Cardiol 81:1339-1344, 1998)

DCM & Muscular Dystrophy

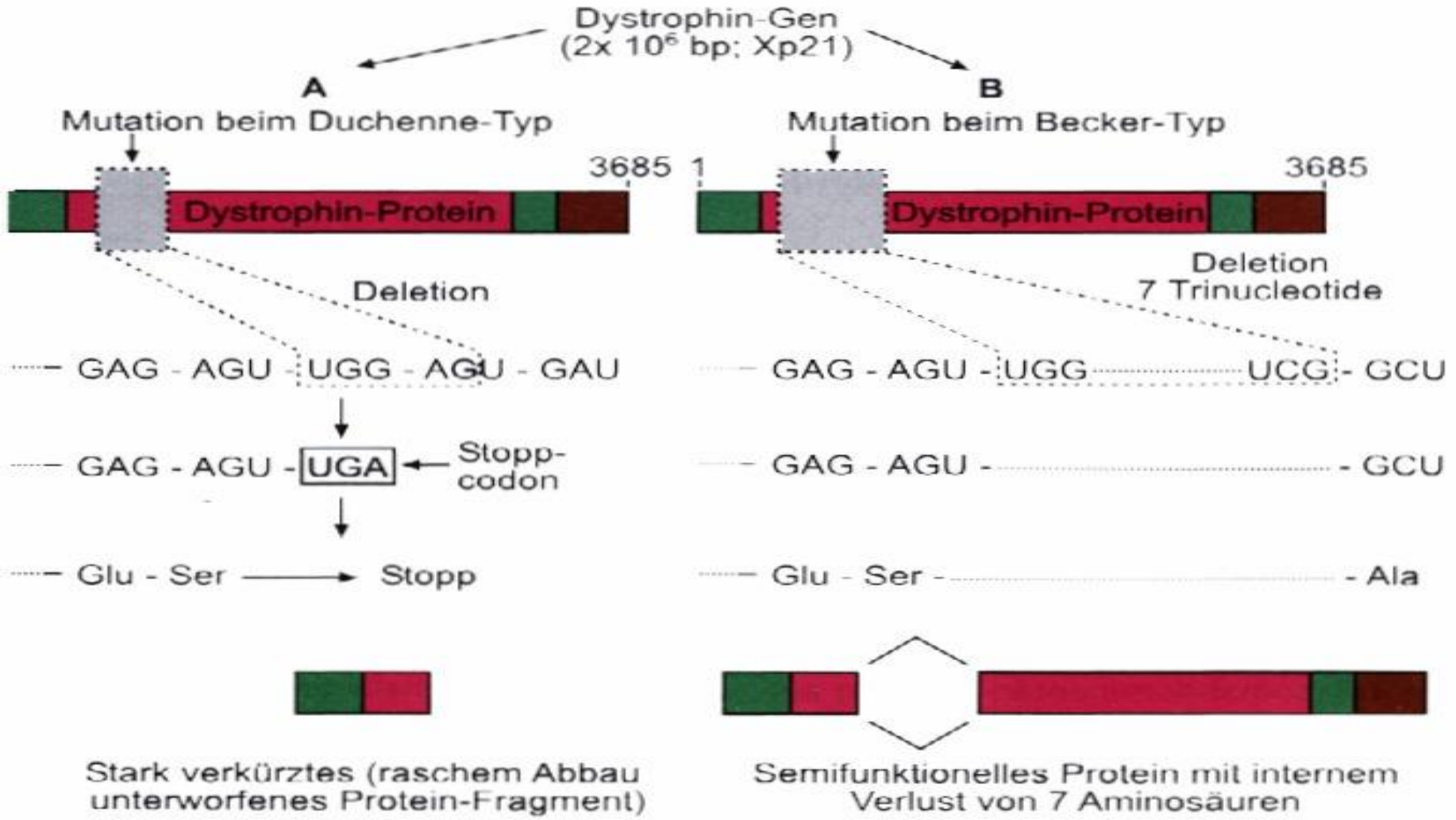
- Some, but not all, cardiomyopathies are associated with muscular dystrophy.

Dystrophin is a structural part of cardiac and skeletal muscle tissues
α-D: α Dystroglycan, DAGC: Dystrophin associated Glycoprotein Complex



(Buddecke, Molekulare Medizin)

Molekulare Basis der unterschiedlichen Verlaufsformen der progressiven Muskeldystrophie



(Buddecke, Molekulare Medizin)

Schwere progressive Verlaufsform

Milde Verlaufsform

(Peter E. Becker, geb 1908, Humangenetiker, Göttingen)

Mutations as a possible cause of DCM

TABLE 59–4 Molecular Defects Linked to the Various Cardiomyopathies

Genomic Defect	Cardiomyopathy		
	Hypertrophic	*Dilated*	*Restrictive*
Sarcomere			
Myosin heavy chain	M	M	
Myosin essential light chain	M		
Myosin regulatory light chain	M		
Cardiac actin	M	M	
Troponin T	M/D	D	
Troponin I	M		M
Alpha-tropomyosin	M	M	
Myosin-binding protein C	M/D		
Titin/titin-related Protein			
Titin	M	M/D	
Telethonin (T-cap)		M	
Z-disk-associated Proteins			
Muscle LIM domain protein		M	
Sarcolemma Cytoskeleton			
Dystrophin		D	
Beta-sarcoglycan		D/Dup	
Delta-sarcoglycan		M	
Alpha-dystrobrevin		M	
Metavinculin		D	
Intermediate Filaments			
Desmin		M	
Lamin A/C		M	

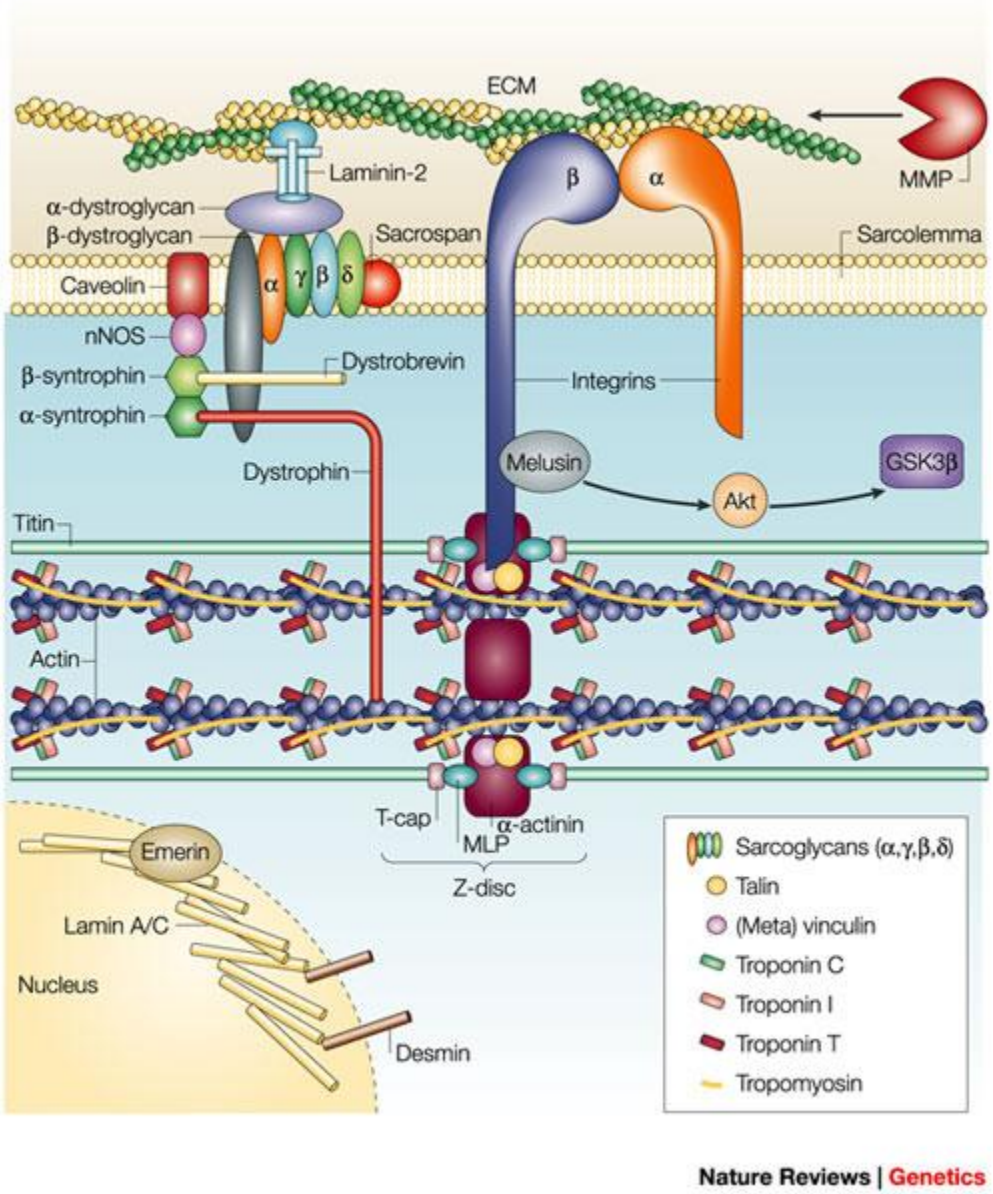
D = deletion; Dup = duplication; M = missense.

Adapted from Chien KR: Genotype, phenotype: Upstairs, downstairs in the family of cardiomyopathies. J Clin Invest 111:175, 2003.

Summary

Location	Mechanism
Extracellular matrix	Different cell types, **particularly endothelial cells**, are affected
Costamer / Integrin interacting signaling molecules	Depending on expression pattern, mutations affect different cell types, including (& primarily) **endothelial cells** Mutations affect survival pathways
Cell membrane / Cytoskeletal (Dystrophin)	Force transduction
Z-disc /Z-disc associated proteins	Mechanosensation & Mechanotransduction, possibly affecting calcium sensitivity
Intermediate Filaments (cytosolic)	Mechanotransduction & Apoptosis
Nucleus, Nuclear membrane	Mechanotransduction & Apoptosis (direct chromatin interaction may directly affect gene expression)
Calcium metabolism	Phospholamban mutations
Sarcomer	Depending on type of mutation probably hypertrophic cardiomyopathy degenerating into dilated cardiomyopathy (indirect DCM pathway) Mutations affect as well directly contractility and calcium sensitivity (direct DCM pathway)
Mitochondrial	Defect in generation of energy
Calcium Sensitivity	Decreased calcium sensitivity and or “unresponsiveness to phosphorylation”

Known DCM-Genes



Liew et al., Nat Rev Gen 2004

Known DCM-Genes

Disease Gene	Symbol	Chromosomal Locus	Comments
Dystrophin β-Sarkoglykan δ-Sarkoglykan α-Dystrobrevin Laminin α	DMD SGCB SGCD DTNA LAMA4	Xp21 4q11 5q33–34 18q12.1–q12.2 6q21	Myopathy, X-linked Myopathy Myopathy Also leftventricular „non compaction“
Desmin Titin Muscle LIM Protein Kardiales Aktin Cypher/ZASP Tinin-cap/Teletonin Integrin Linked Kinase Nebulette Calsarcin-1/Myozenin-2	DES TTN MLP/CSRP3 ACTC LDB3 TCAP ILK NEBL MYOZ2	2q35 2q31 11p15.1 15q14 10q23.2 17q12 11p15.4-p15.5 10p12 4q26	Myopathy Also LV-“non compaction“
Kardiales Troponin T Kardiales Troponin C Kardiales Troponin I β-Myosin-Schwerkette α-Tropomyosin	TNNT2 TNNC1 TNNI3 MYH7 TPM1	1q32 3q21.1 19q13.42 14q11.2–13 15q22	
Lamin A/C EYA4	LMNA EYA4	1q1–q21 6q23–q24	Conduction defect, Myopathy Myopathy, Deafness
Desmoplakin Metavinculin	DSP MVCL	6p23–p24 10q22–q23	„Wololy hair“, Keratodermatose Mitrall valve prolapse
Natriumkanal Typ V ATP-sensitiver Kaliumkanal Phospholamban	SCN5A ABCC9/SUR2A PLN	3q22.2 12p12.1 6q12-q16	Conduction defect
G4.5/Tafazzin Mitochondriale DNA	TAZ	Xq28 mtDNA	Barth-Syndrome, X-linked, congenital DCM, LV „non compaction“

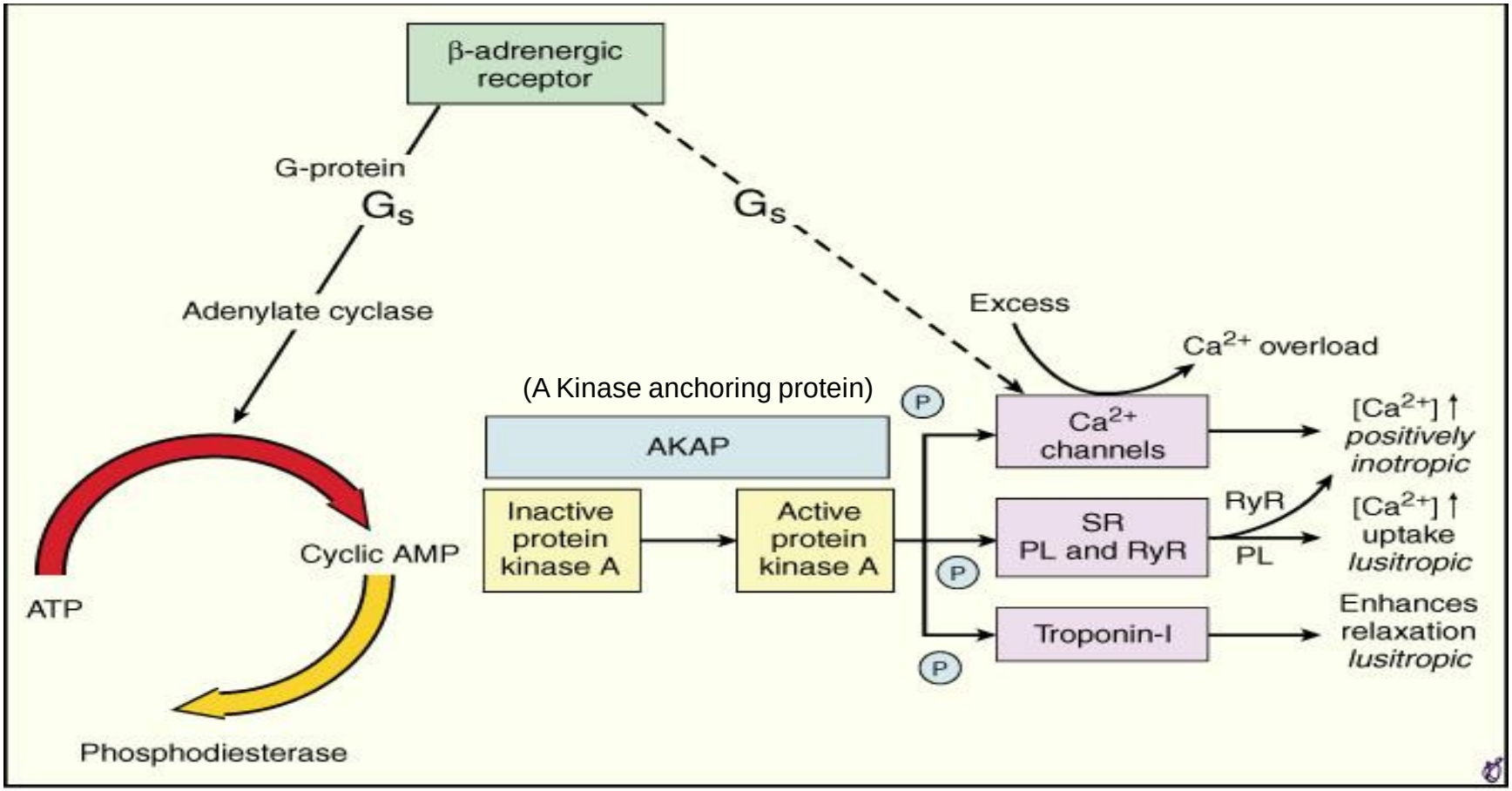
Inheritance	phenotype	locus	gene	protein
Autosomal dominant	pure DCM	9q12–q13	?	
	pure DCM	1q32	?	
	pure DCM	2q24.3–q31	*TTN*	titin
	pure DCM	6q12–q16	?	
	pure DCM	2q35	*DES*	desmin
	pure DCM	5q33	*SGCD*	δ-sarcoglycan
	pure DCM	15q11– qter	*ACTC*	actin
	pure DCM, early onset	14q11.2	*MYH7*	β-myosin heavy chain
	pure DCM, early onset	1q32	*TNNT2*	cardiac troponin T
Autosomal dominant +	DCM + CD	1q21	*LMNA*	lamin A/C
	DCM + CD	2q14–q22	?	
	DCM + CD + SND	3p22–p25	?	
	DCM + MVP	10q21–q23	?	
	DCM + hearing loss	6q23–q24	*EYA4*	eyes absent 4
	DCM + CD + LGMD	6q22–q23	?	
	DCM + CD + MD (AD-EDMD)	1q21	*LMNA*	lamin A/C
	DCM + CD + LGMD (LGMD1B)	1q21	*LMNA*	lamin A/C
Autosomal recessive	LGMD +/– cardiomyopathy	17q21	*SGCA*	α-sarcoglycan
	LGMD + severe cardiomyopathy	4q12	*SGCB*	β-sarcoglycan
	LGMD + cardiomyopathy (Brazil)	5q33	*SGCD*	δ-sarcoglycan
X-linked	Pure DCM	Xp21.3	*DYS*	dystrophin
	DCM lethal in infancy	Xq28	*TAZ*	tafazzin
	DCM + myopathy (Barth-Syndrome)	Xq28	*TAZ*	tafazzin
	DCM + CD + MD (XL-EDMD)	Xq28	*EMD*	emerin

Abbreviations: DCM, dilated cardiomyopathy; CD, conduction defect; SND, sinus node dysfunction; MVP, mitral valve prolapse; LGMD, limb girdle muscular dystrophy; MD, muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; AD, autosomal dominant; XL, X-linked.

Left ventricular non-compaction

- Left ventricular non-compaction cardiomyopathy is a heart muscle condition in which the muscular wall of the main pumping chamber of the heart (the left ventricle) appears to be spongy and “non-compacted”, consisting of a meshwork of numerous muscle bands (trabeculations).
- This type of cardiomyopathy has not been fully understood so far and remains unclassified by the World Health Organisation, although it is thought to have some individual features. Its cause, development, clinical course and treatment are fields of ongoing research (the Cardiomyopathy Association).

β-receptor mutations, polymorphisms and antibodies against the β-receptor



Additional Causes: Myocarditis

- Viral myocarditis – another possible cause of DCM: Adenovirus, Picorna Viru, Coxsackie Virus
- Diagnosis based on the analysis of endomyocardial biopsies (Histology, Detection of viralen DNA and RNA via PCR and/or in situ Hybridisation) in addition to antibody titers, markers of inflammation
- Between 15% and 70% of all DCM cases are probably due to myocarditis

Autoimmune Disease – another cause of DCM

- Defects in cellbased as well as in humoral immunity have been found in DCM
- Theory: viral proteins will be integrated into the cardiomyocyte cellmembrane, finally leading to the induction of auto-antibodies.
- Anti β myosin heavy chain, anti β receptor, anti mitochondrial protein antibodies have been found in patients affected by DCM
- Immunadsorption (i. e. Removal of antibodies) has been shown to improve myocardial function in DCM patients.

Additional causes – toxins, drugs

- Anthracyclines, particularly Doxorubicin (Chemotherapy)
- Alcohol – toxic cardiomyopathy
- Cocain
- HIV Infection und consecutive DCM

Prognosis

TABLE 59–3 Factors Associated with an Adverse Outcome in Dilated Cardiomyopathy

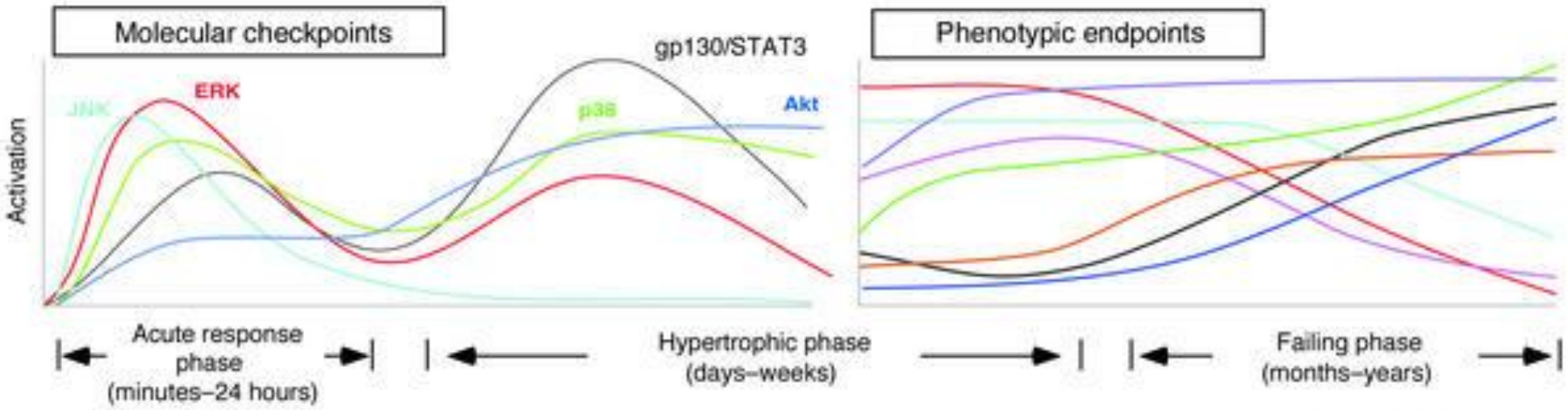
Clinical	Noninvasive	Invasive
NYHA Class III/IV	Low LV ejection fraction	High LV filling pressures
Increasing age	Marked LV dilation	
Low exercise peak oxygen consumption	Low LV mass	
Marked intraventricular conduction delay	≥Moderate mitral regurgitation	
Complex ventricular arrhythmias	Abnormal diastolic function	
Abnormal signal-averaged ECG	Abnormal contractile reserve	
Evidence of excessive sympathetic stimulation	Right ventricular dilation or dysfunction	
Protodiastolic gallop (S_3)		

ECG = electrocardiogram; LV = left ventricular; NYHA = New York Heart Association.

TABLE 20–3 Two Pathways of Ventricular Dilation and Increased Filling Pressure

Hemodynamic (Acute)
Dilation and increased end-diastolic pressure caused when increased venous return or decreased ejection increases end-diastolic volume. This form of dilation occurs when physiological (functional) signaling increases sarcomere length, which increases the heart's ability to perform work (Starling law of the heart)
Architectural (Chronic)
Dilation and increased filling pressures caused when hypertrophy increases cardiac myocyte length and alters passive muscle properties. By increasing wall stress, this growth response increases the energy demands of the heart and decreases cardiac efficiency, initiating a vicious circle that worsens heart failure. This form of dilation occurs when abnormal transcriptional (proliferative) signaling causes eccentric hypertrophy (systolic dysfunction), and it tends to progress (remodeling)

Adapted from Katz A: Ernest Henry Starling, his predecessors, and the "law of the heart." Circulation 106:2986, 2002.



Gene expression profiles

(Acute phase)

Upregulation

c-fos
c-jun
junB
egr-1
nur77
BNP
SOCS3

(Hypertrophic-failing phase)

Upregulation

Secreted proteins
ANF, Lipocortin I, ET-1
HB-EGF, TGF-β1, BNP
Osteoblast-specific factor 2
Cytoskeletal proteins
αMHC, βMHC
MLC1a/v, MLC2a
MLC2v, Tropomyosin
Troponin C, Myomesin
Smooth muscle α–actin
Skeletal α–actin
α–cardiac actin
FHL1 (HCM), Sarcosin
Desmin, Gelsolin,
Extracellular matrix
Fibulin, Fibronectin
Laminin, Collagen
Others
Heat shock 70 kDa proteins 1, 6, 8
Quaking protein, CARP

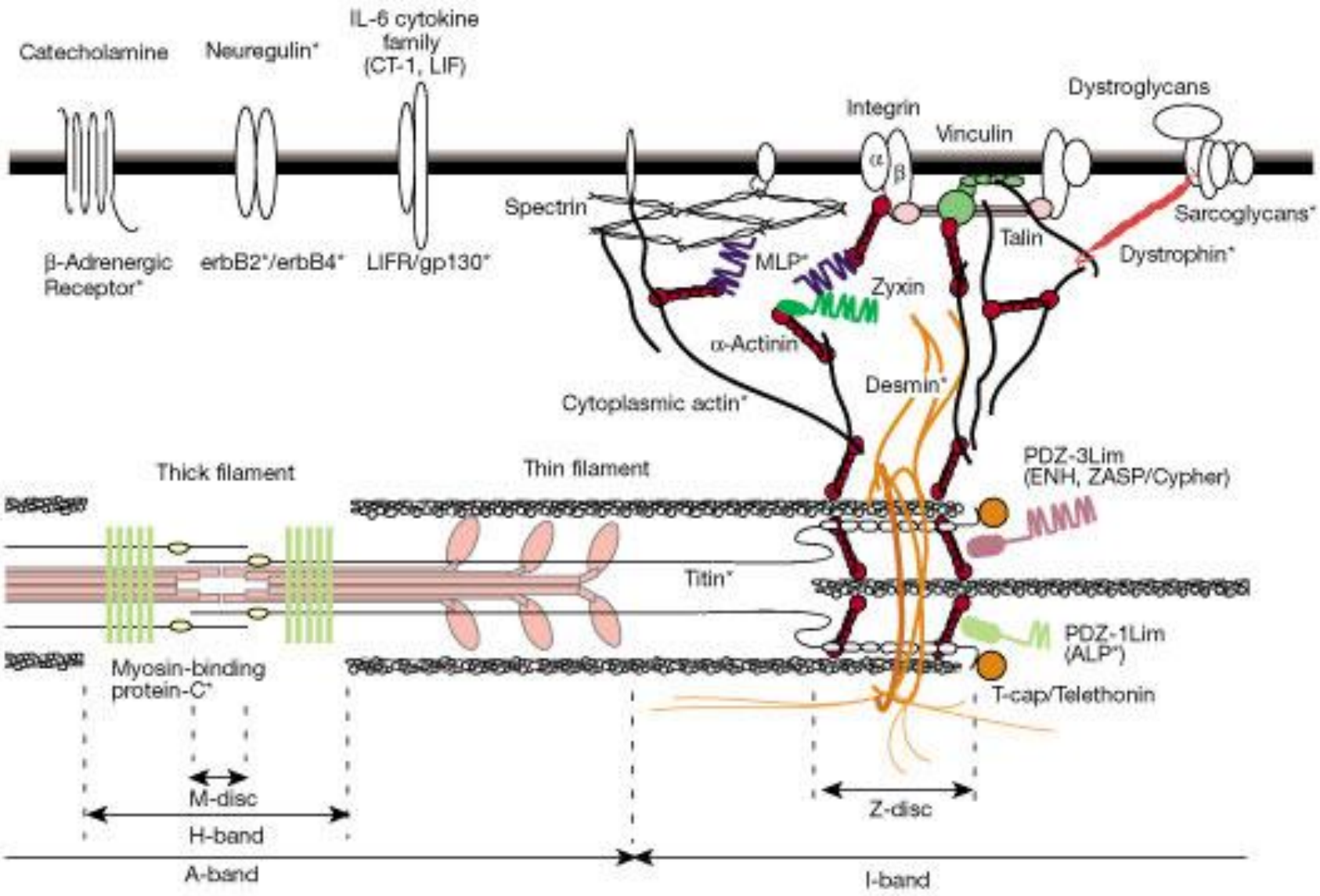
Metabolism/translation
Ubiquitin, Pyruvate dehydrogenase α
NADH ubiquinone oxidoreductase
Creatin kinase, Myoglobin
Phosphorylase kinase catalytic subunit
Superoxide dismutase 2
Aldose reductase, EF-1a, EF-2, IF-4AII
28S, 60S ribosomal L3
Ion-channels/carriers
Na^+/Ca^{2+} exchanger, Kv1.4
Voltage-dependent anion channel-1
Signaling
Gsα, βARK, Adenylyl cyclase VII
A-kinase, C-kinase inhibitor-1, ILK
Rap1B, SOCS3, Id-1, GATA-4
SP1/3, PGD/D2 synthase

Downregulation

Cytoskeletal proteins
FHL1 (failing heart)
Nonsarcomeric MLC2
Ion-channels/carriers
L-type Ca^{2+} channel
SERCA2
Phospholambam
Kv4.2, 4.3
Kv1.5
KChIP2
Signaling
type-A like Ephrin receptor
Others
α1-Antichymotrypsin
αB-Crystallin
Plasminogen activator inhibitor-1
TIM17

Contractility
Chamber size
Wall thickness
Left ventricular end diastolic pressure
Left ventricular end systolic pressure
Arrhythmia (e.g., AF, VT, AVB)
Myocyte dropout Replacement fibrosis
Embryonic gene program

Strukturelle Organisation von Kandidatengenen der Dilatativen Kardiomyopathie



(Chien, Nature 2000)

Gene Regulation in Heart Failure

Acute phase - upregulation of:

- c-fos
- c-jun
- junB
- egr-1
- nur 77
- BNP
- SOCS3

Hypertrophic – Failing Phase

Upregulation:

Secreted proteins:

- ANF, Lipocortin I, ET-1, HB-EGF, TGF-β1, BNP,
- Osteoblast-specific factor 2

Cytoskeletal proteins:

- αMHC, βMHC, MLC1a/v, MLC2a
- MLC2v, Tropomyosin
- Troponin C, Moymesin
- Smooth muscle α-actin
- Skeletal α-actin
- α-cardiac actin
- FHL1 (HCM)m Carcosin, Desmin, Gelsolin

Extracellular matrix:

- Fibulin, Fibronectin
- Laminin, Collagen

Others:

- Heat shock 70 kDa proteins 1, 6, 8
- Quaking protein, CARP

Metabolism/translation:

- Ubiqutin, Pyruvate dehydrogenase αNADH ubiquinone oxidoreductase
- Creatinin kinase, Myoglobin
- Phosphorylase kinase catalytic subunit
- Superoxide dismutase 2
- Aldose reductase, EF-1a, EF-2, IF-4AII
- 28S, 60S ribo´somal L3
- Ion-channels/carriers
- Na+/Ca 2+ exchanger, Kv1.4
- Voltages-dependent anion channel-1

Signalling:

- Gsα, βARK, Adenylyl cyclase VII
- A-kinase, C-kinase inhibitor-1, ILK
- Rap1B, SOCS3, Id-1, GATA-4
- SP1/3, PDG/D2synthase

Downregulation

Cytoskeletal proteins

- FHL1 (failing heart)
- Nonsarcomeric MLC2

Ion-channels/carriers

- L-type Ca2+ channel
- SERCA2
- Phospholamban
- Kv4.2, 4.3
- Kv1.5
- KChIP2

Singnalling

- type-A-like Ephrin receptor

Others

- α1 Antichymotrypsin
- αB-Crystallin
- Plasminogen activator inhibitor-1
- TIM17

- Hypertrophic-failing phase
- Secreted proteins ANF, Lipocortin I, ET-1, HB-EGF, TGF-β1, BNP,
- Osteoblast-specific factor 2
- Cytoskeletal proteins
- αMHC, βMHC, MLC1a/v, MLC2a
- MLC2v, Tropomyosin
- Troponin C, Moymesin
- Smooth muscle α-actin
- Skeletal α-actin
- α-cardiac actin
- FHL1 (HCM)m Carcosin, Desmin, Gelsolin
- Extracellular matrix
- Fibulin, Fibronectin
- Laminin, Collagen
- Others
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- Phosphorylase kinase catalytic subunit
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- 28S, 60S ribo´somal L3
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- Gsα, βARK, Adenylyl cyclase VII
- A-kinase, C-kinase inhibitor-1, ILK
- Rap1B, SOCS3, Id-1, GATA-4
- SP1/3, PDG/D2synthase

TABLE 20–2 Definitions of Terms Used to Describe Systolic and Diastolic Function

Term	Definition
Preload	Distending force of the ventricular wall, which is highest at end-diastole and is responsible for sarcomere length at the beginning of systolic contraction
Afterload	Resisting force of the ventricular wall during systolic ejection, which is necessary to overcome peripheral vascular resistance or impedance; measures of afterload are peak-systolic, mean-systolic, or end-systolic wall stress
Contractility	Intrinsic ability of the myocardium to generate force at a certain rate and time (controlled for loading conditions)
Cardiac output	Stroke volume multiplied by heart rate
Stroke work	Mean systolic blood pressure multiplied by stroke volume
Stroke force	Stroke work per ejection time
Stress	Force per area
Wall stress	Pressure multiplied by radius, divided by wall thickness × 2
Compliance or distensibility	Change in volume per change in pressure (dV/dP)
Elastance	Slope of the end-systolic pressure-volume relation
Elasticity	Property of a material to restore its initial length or geometry after distending force has been removed
Strain	Length change in percent of initial length; two definitions are used: LaGrangian strain $e = (l - l_o)l_o$ and natural strain $e = \ln(l/lo)$
Stiffness	Pressure per volume change (dP/dV). *Ventricular stiffness* is a measure for changes of the ventricle as a whole; *myocardial stiffness* is a measure for changes of the myocardium itself. Ventricular properties are characterized by instantaneous pressure-volume relations, whereas myocardial properties are best described by stress-strain relations.
Creep	Time-dependent lengthening of a material in the presence of a constant force
Stress relaxation	Time-dependent decrease of stress in the presence of a constant length
Viscoelasticity	Resistance of a material to length changes (strain) or the velocity of length changes (strain rate)

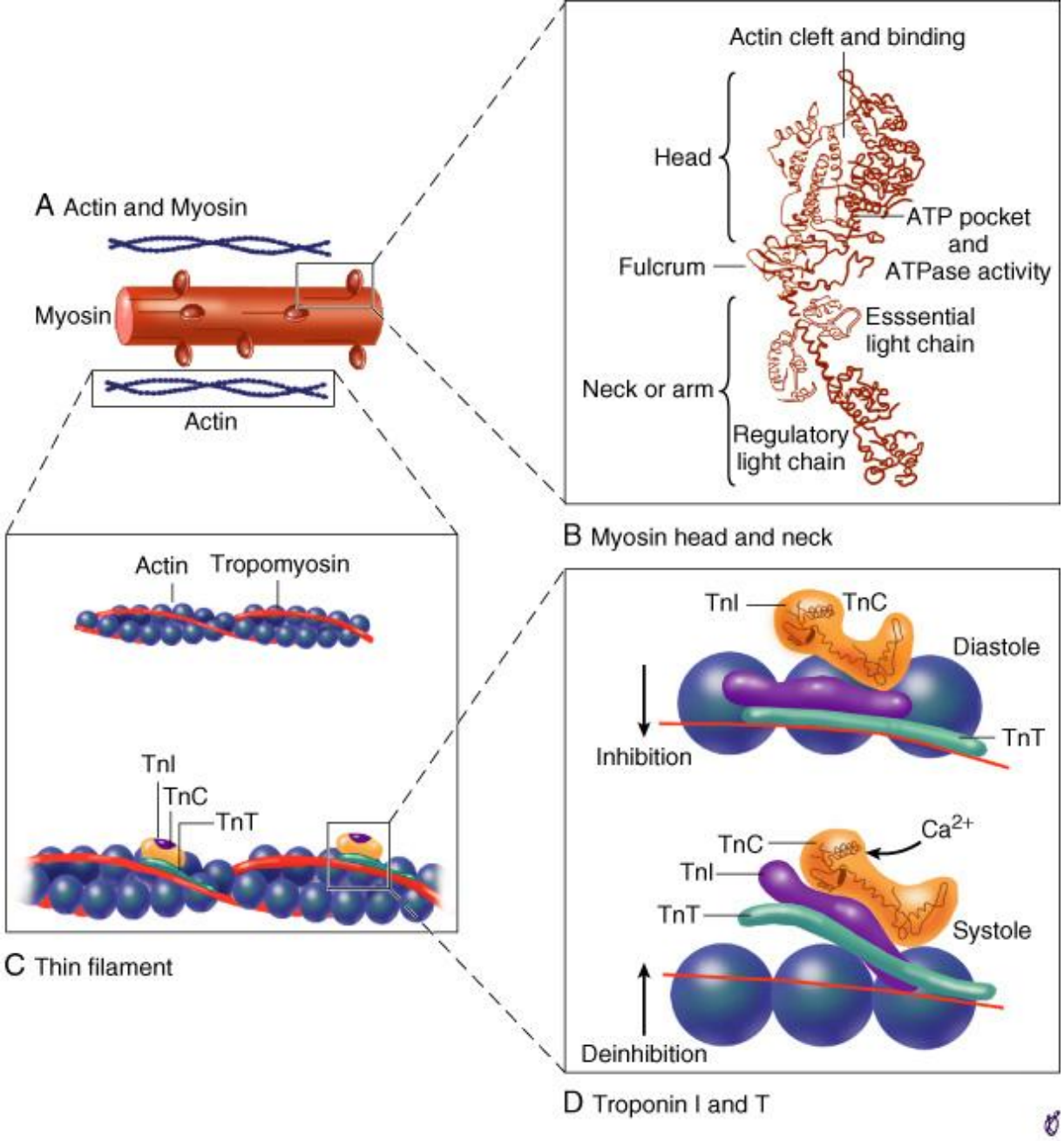
TABLE 20–8 Age-Related Differences in LV and Arterial Coupling in Patients with Dilated Cardiomyopathy

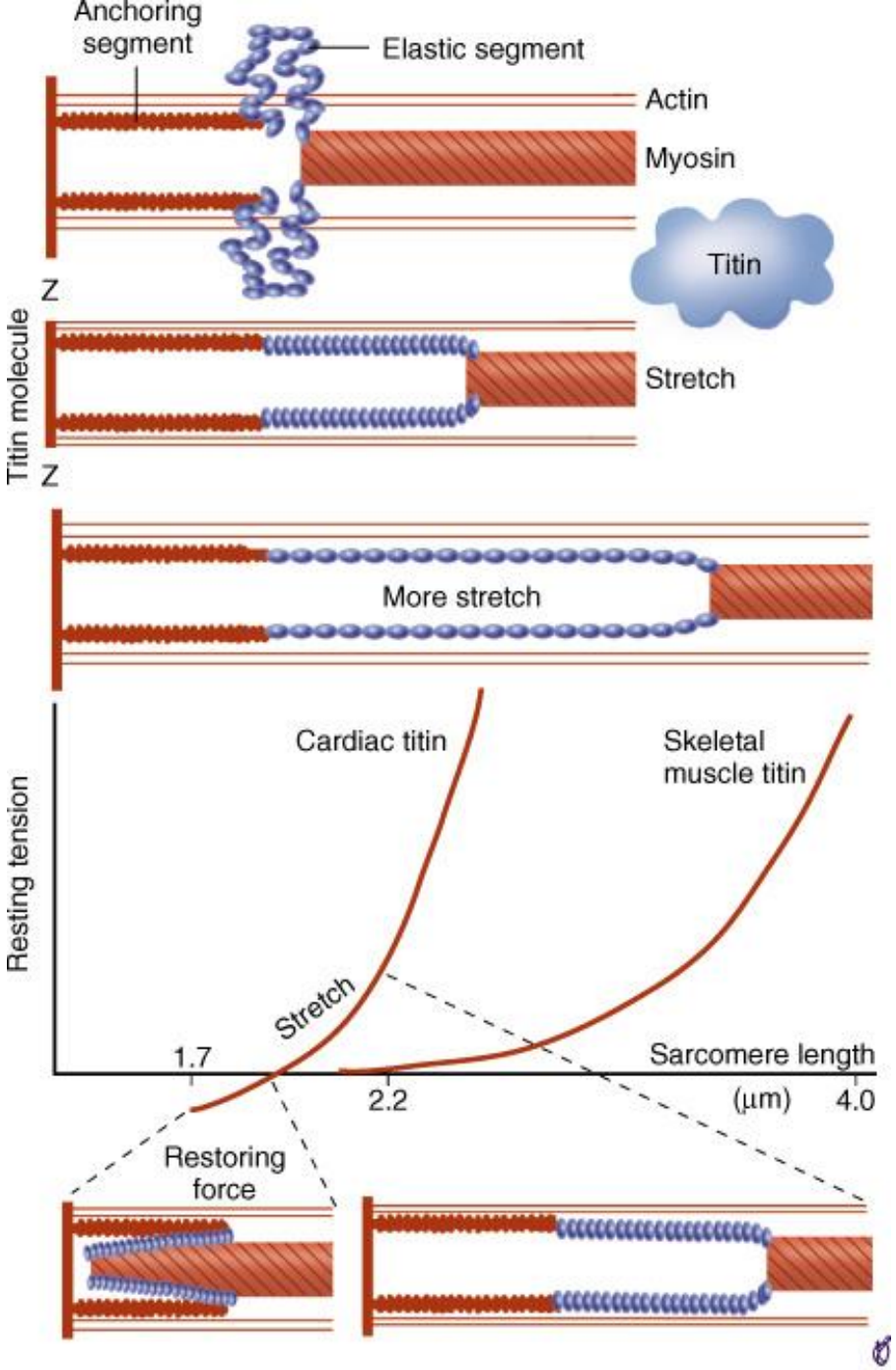
Parameters	Young Patients <35 yr	Intermediate-Aged Patients 35-50 yr	Older Patients >50 yr
Maximum + dP/dt (mm Hg/sec)	1011 ± 160	1170 ± 159	1147 ± 374
Stroke work (g-m/m^2)	19 ± 10	20 ± 10	19 ± 10
Pulse pressure (mm Hg)	26 ± 8	30 ± 11	38 ± 10
Pulse wave velocity (m/sec)	4.7 ± 0.4	6.5 ± 0.9	7.9 ± 0.6
Systemic vascular resistance (dyn-sec · cm^{-5})	1872 ± 789	2373 ± 762	2440 ± 770
Arterial compliance (ml/mm Hg)	1.33 ± 0.63	0.72 ± 0.40	0.51 ± 0.17

LV = left ventricular.

Adapted from Carroll JD, Shroff S, Arand P, et al: Arterial mechanical properties in dilated cardiomyopathy. J Clin Invest 87:1002-1009, 1991.

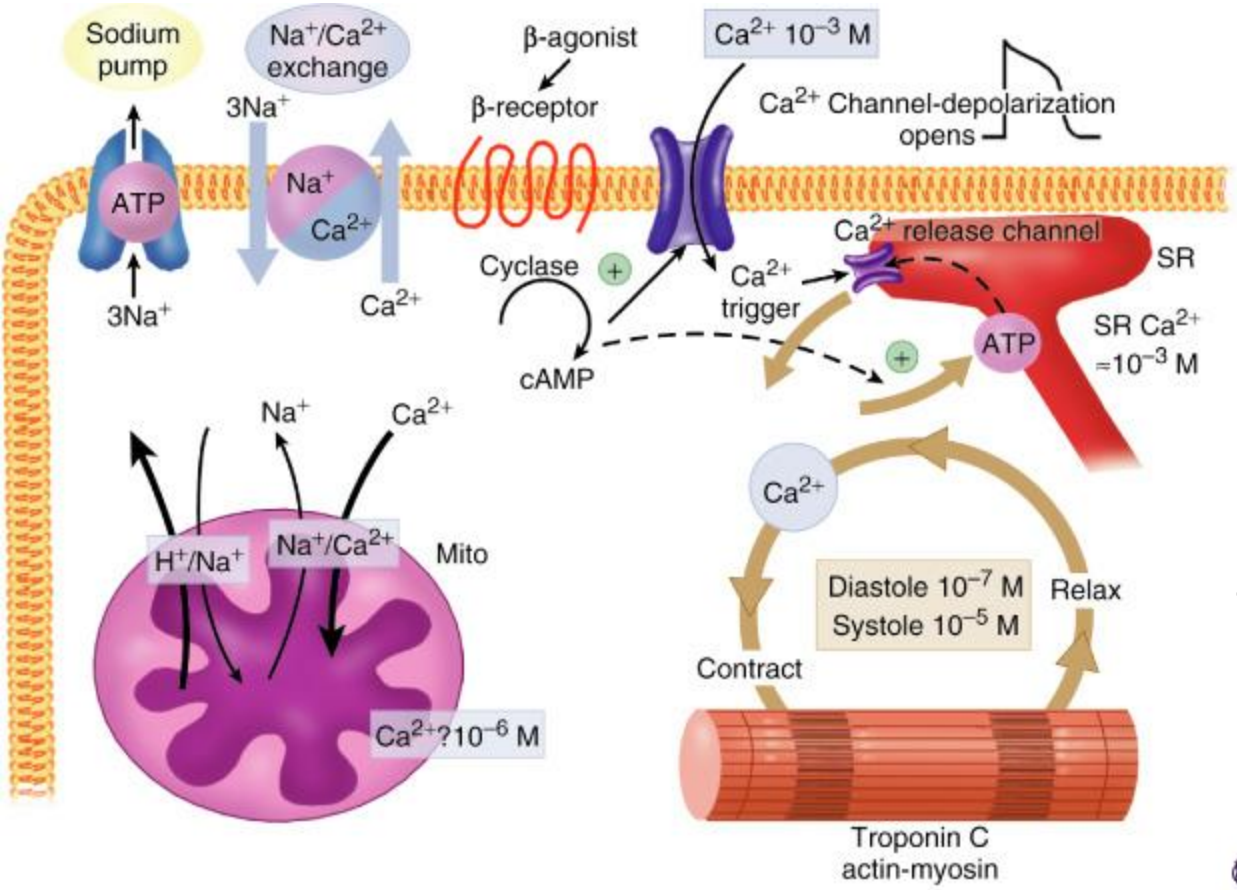
Acto-myosin Interaction





Titin

Calcium fluxes in the myocardium



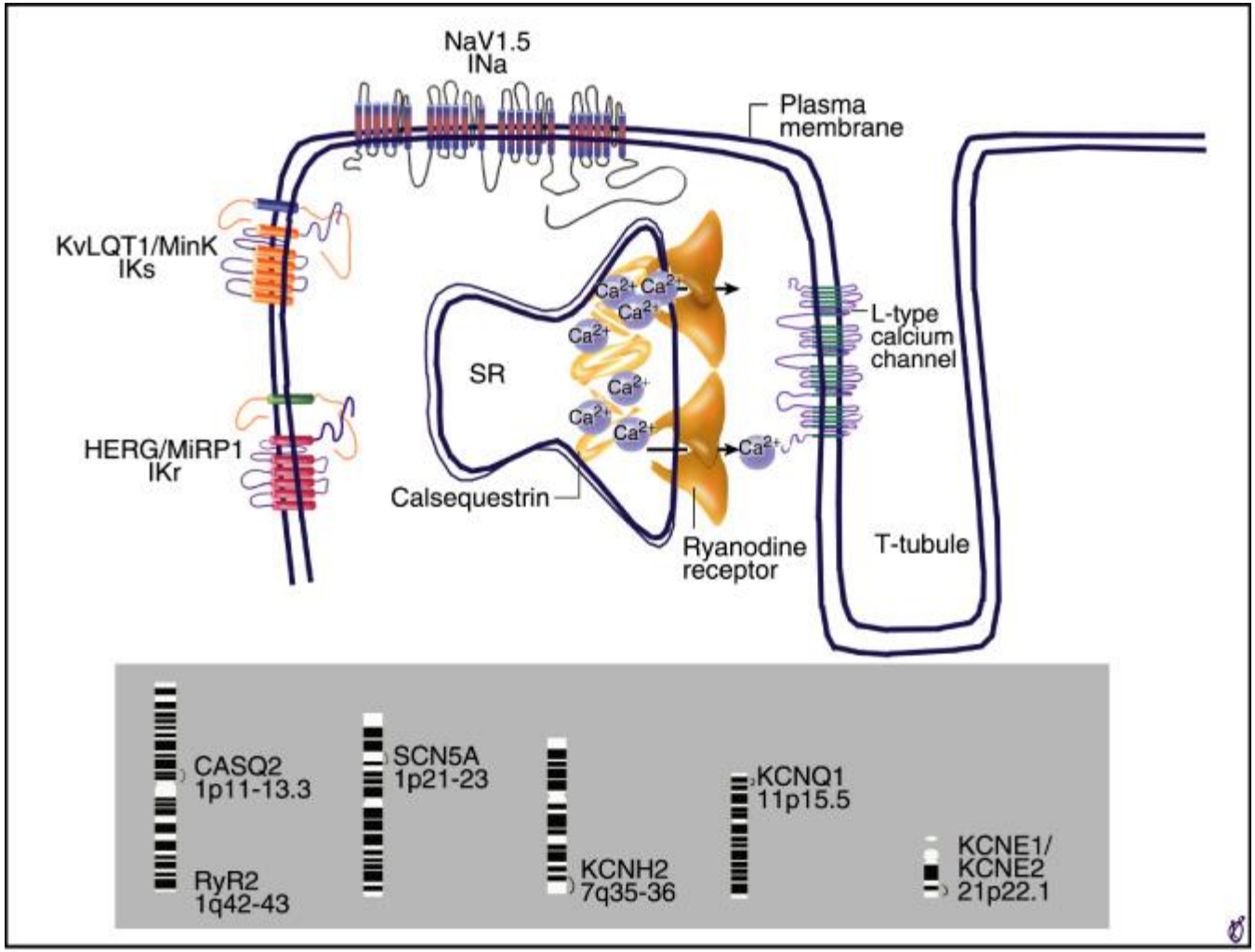
1. L-type calcium channel increases intracellular calcium and induces „calcium induced calcium release“
2. cAMP increase through β adrenergic stimulation increases
   a) Calcium influx through the calcium channel
   b) Increase the rate of calcium uptake into the SR
3. Exit of calcium ions through the Na/Ca exchanger and removal of Na via the Na channel

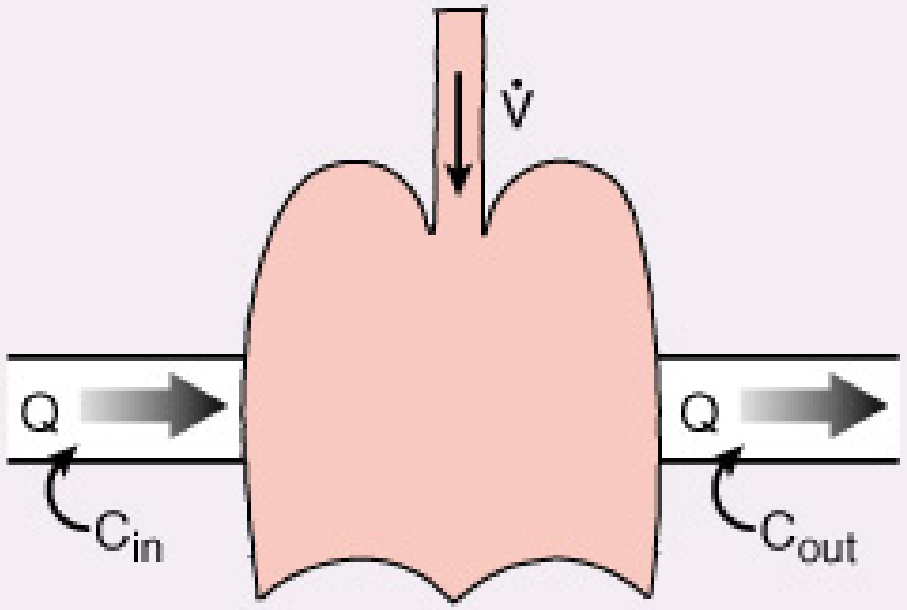
Mitochondria can act as a buffer for calcium concentrations.

Dilatative Kardiomyopathie (DCM) – mutierte Gene, Beispiele

Gen	**Zahl der bekannten Mutationen**	**Mutation (Beispiel)**	**Komponente der Kardiomyozyte**
Schwere Kette des β MHC			Sarkomer
Desmin			Intermediäres Filament
Muskel LIM Protein	1	W4R	Z-Scheibe
δ Sarkoglykan			Transmembranäres Protein
Myosin bindendes Protein C			Sarkomer
Dystrophin			Intermediäres Filament
Mitochondriale Gene			Mitochondrien

Genes and proteins in inherited arrhythmogenic diseases: the chromosomal locations of the genes known to cause cardiac inherited disorders. The proteins encoded by each gene are schematically drawn in the figure.





Rate of indicator out = rate in + rate added

$$Q \times C_{out} = Q \times C_{in} + \dot{V}$$

$$Q = \frac{\dot{V}}{(C_{out} - C_{in})}$$

When O_2 is used as indicator:

$$Q = \frac{\dot{V}O_2}{C_A\,O_2 - C_V\,O_2}$$

Das waren tolle Zeiten!

William Harvey, der Erstbeschreiber des geschlossenen Blutkreislaufs, erklärt den politisch verantwortlichen seine Wissenschaft


EXERCITATIO
ANATOMICA DE
MOTV CORDIS ET SAN-
GVINIS IN ANIMALI-
BVS,
GVILIELMI HARVEI ANGLI,
Medici Regii, & Professoris Anatomiæ in Col-
legio Medicorum Londinensi.
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI.
ANNO M. DC. XXVIII.

Frankfurt, 1628

Harvey explains to the King
Robert Hannah, 1848

Thank you very much for your attention!