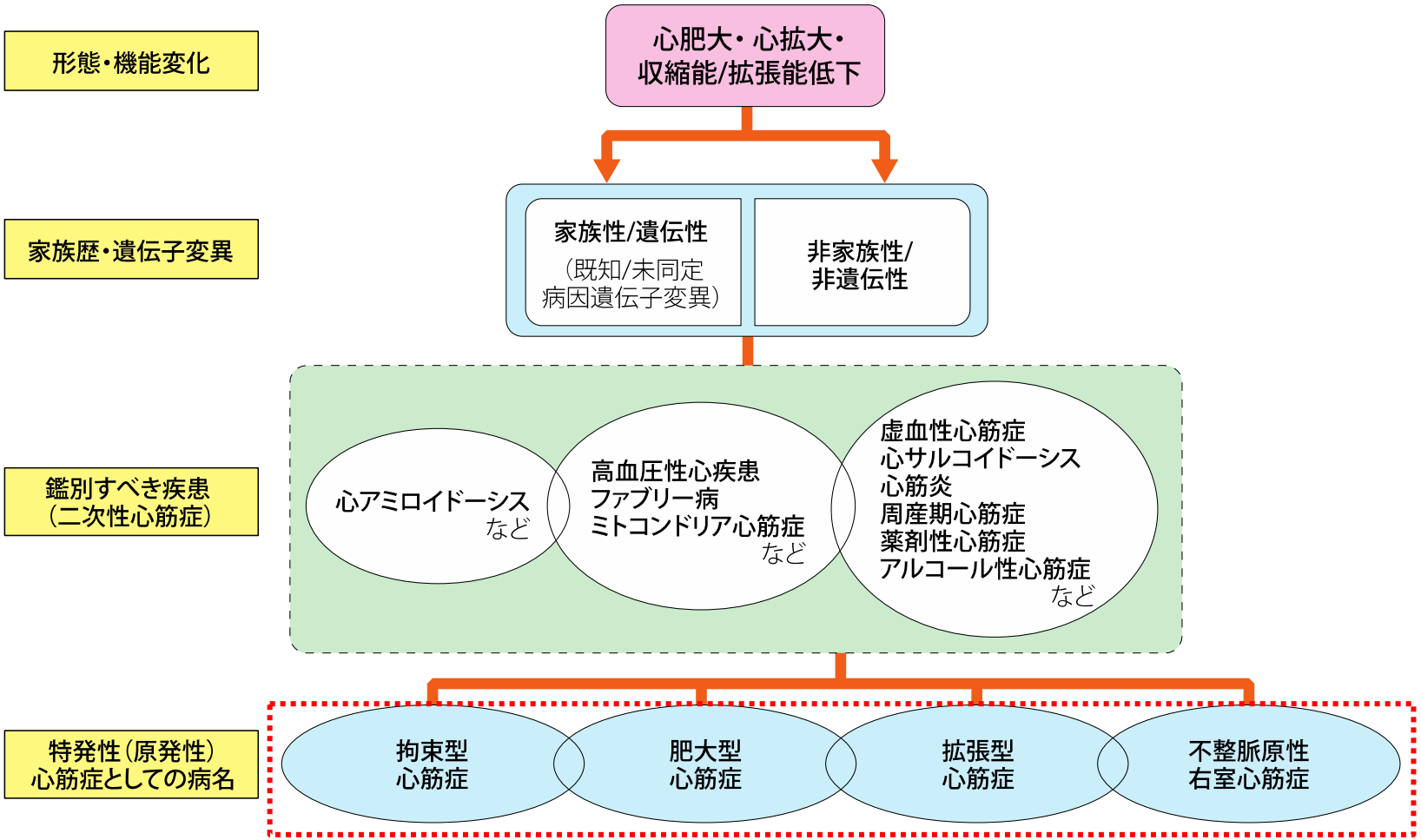
遺伝子異常と小児心筋疾患

国立循環器病研究センター
教育推進部・小児循環器部

白石　公

心筋症の定義と分類 -JCS心筋症診療ガイドライン2018

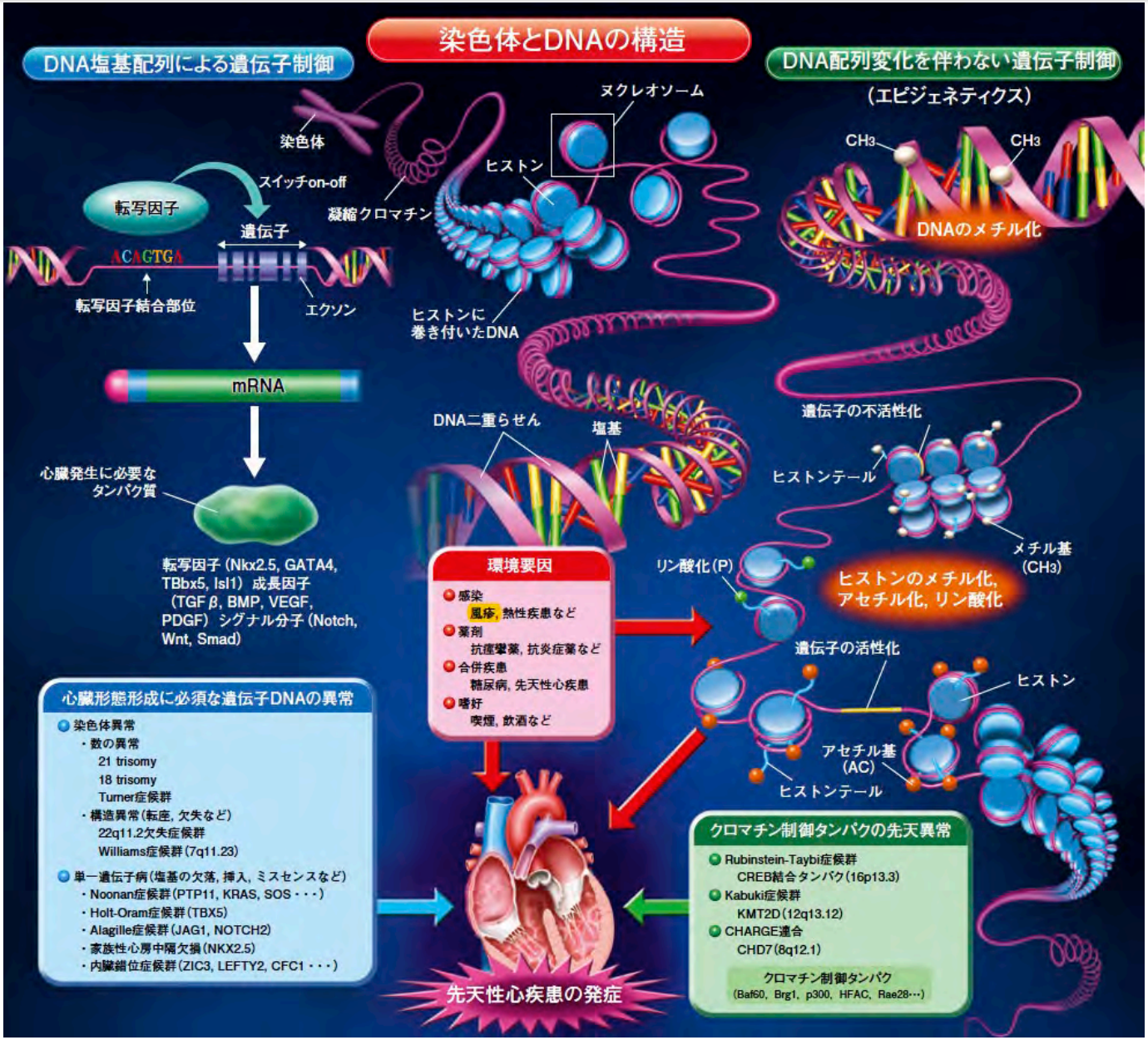


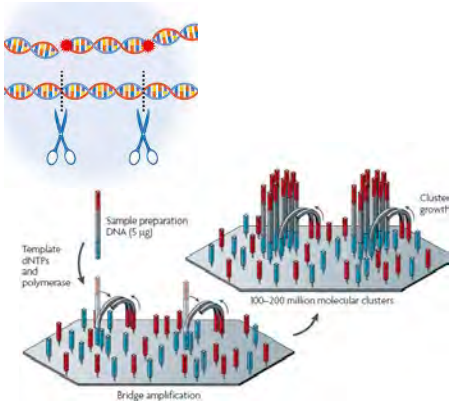
・円の重なりは一部重複した病態を示す.
・点線内は, 特定心筋疾患に該当する.

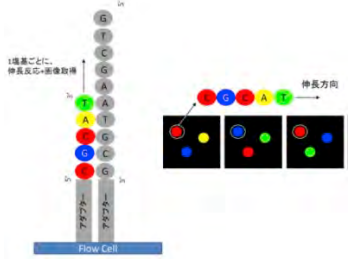
*4つの基本病態に分類できない心筋症を分類不能心筋症（unclassified cardiomyopathy）とする.

日本循環器学会心筋症診療ガイドライン（2018年改訂版）

先天性心疾患で見られる染色体とDNAの構造異常





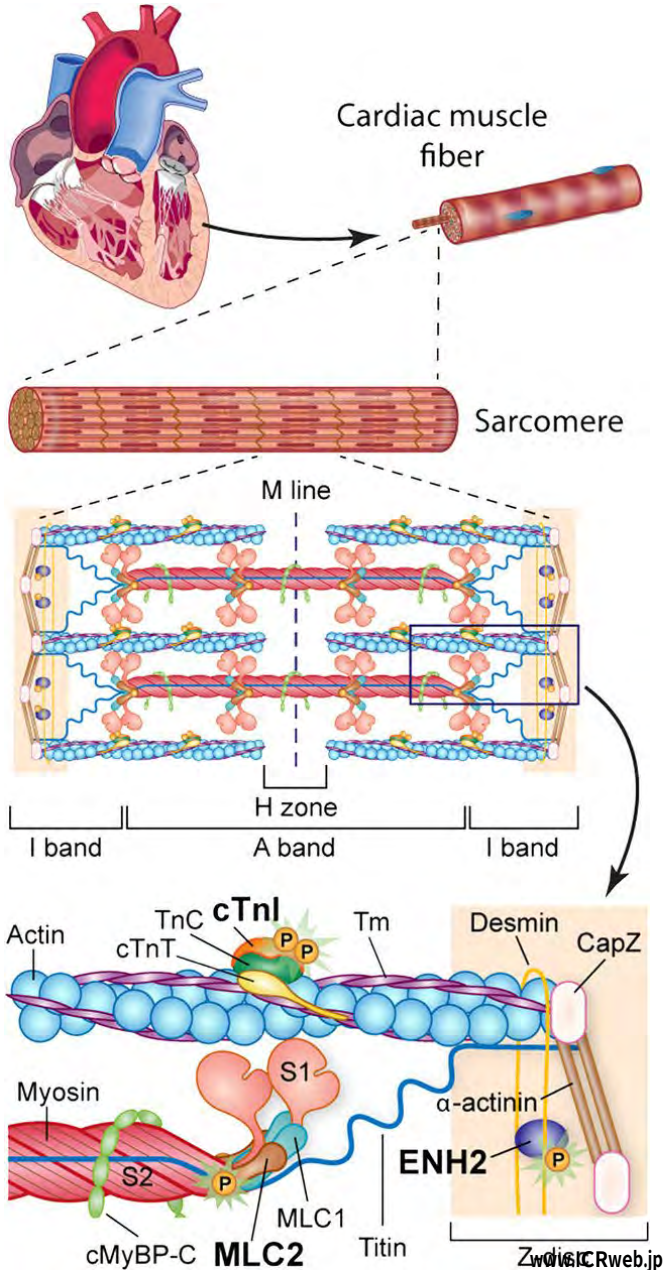


白石. Fetal & Neonatal Medicine 2015;7:95-6.

心筋症に見られる遺伝子異常とsarcomere構造

Phenotypes	Protein	Gene symbol	Frequency in mutated patients	Ref.
Hypertrophic Cardiomyopathy	Beta Myosin heavy chain	*MYH7*	25-35%	16, 63
	Myosin binding protein C, cardiac	*MYBPC3*	30-50%	16, 63
	Cardiac troponin T	*TNNT2*	5-7%	16, 63
	Cardiac troponin I	*TNNI3*	3-5%	16, 63
	Myosin, light chain 2, regulatory	*MYL2*	~3-5%	16
	Myosin, light chain 3, essential	*MYL3*	~2%	16
	Alpha Tropomyosin, Alpha Myosin heavy chain, Titin, Cardiac Actin, Telethonin, Myozenin	*TPM1, MYH6, TTN, ACTC1, TCAP, MYOZ2*	rare	
Dilated Cardiomyopathy	Lamin A/C	*LMNA*	5- 10%	27-63
	Beta Myosin heavy chain (β MHC)	*MYH7*	~7%	27
	Cardiac troponin T (cTNT)	*TNNT2*	~4%	27
	Myosin binding protein C, cardiac (cMyBPC3)	*MYBPC3*	~1%	27
	Sodium channel, type V, α subunit	*SCN5A*	5-10%	63
	Cardiac troponin I (cTNI)	*TNNI3*	~1%	27
	Myosin, light chain 2, regulatory	*MYL2*	~1%	
	Myosin, light chain 3, essential	*MYL3*	~1%	
	Desmin	*DES*	~3%	
	BCL2-associated athanogene 3	*BAG-3*	~3%	
	Alpha Tropomyosin, Titin, Cardiac Actin, Telethonin, Myozenin,	*TPM1, TTN, ACTC1, TCAP, MYOZ2*	~2%	
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Plakophilin 2	*PKP2*	11-43%	20-59
	Desmoglein 2	*DSG2*	12-40%	20-59
	Desmoplakin	*DSP*	6-16%	20-59
	Desmocollin 2	*DSC2*	rare	20-59
	Junction plakoglobin	*JUP*	rare	20-59
	Ryanodine receptor 2	*RYR2*	rare	20-59
	Transmembrane protein 43	*TMEM43*	rare	20-59

Syndromic Cardiomyopathy	Protein	Gene symbol	Inheritance	
HCM+WPW(Wolff Parkinson White)	Protein kinase, AMP-activated, γ 2	*PRKAG2*	Autosomal Dominant	
Danon disease	Lysosomal-associated membrane protein 2	*LAMP2*	X linked	
Pompe disease	alpha Glucosidase	*GAA*	Recessive	
Fabry disease	alpha Galactosidase	*GLA*	X Linked	
Friedreich syndrome	Frataxin	*FXN*	Recessive	
Marfan Syndrome	Fibrillin 1	*FBN1*	Dominant	

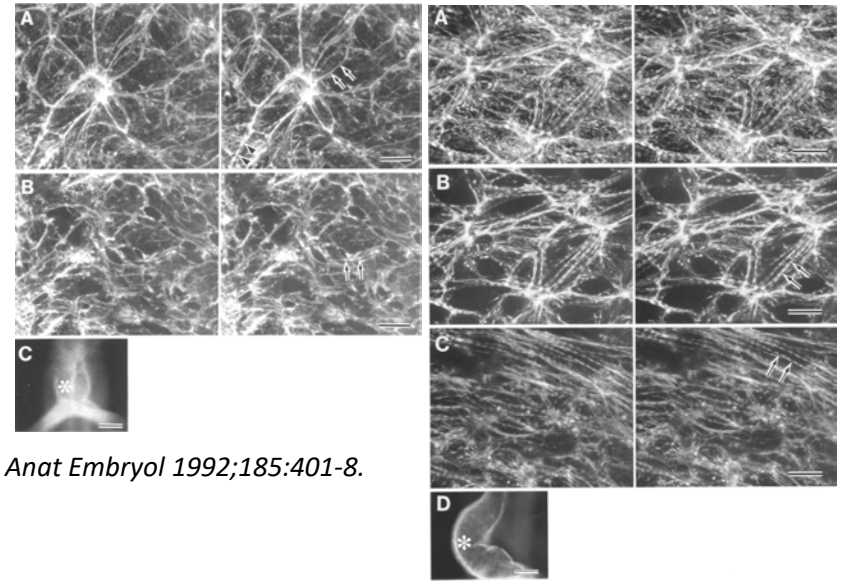


Pascale Richard et al. Br J Sports Med 2012;46:i59-i68

筋原線維の形成過程とその異常

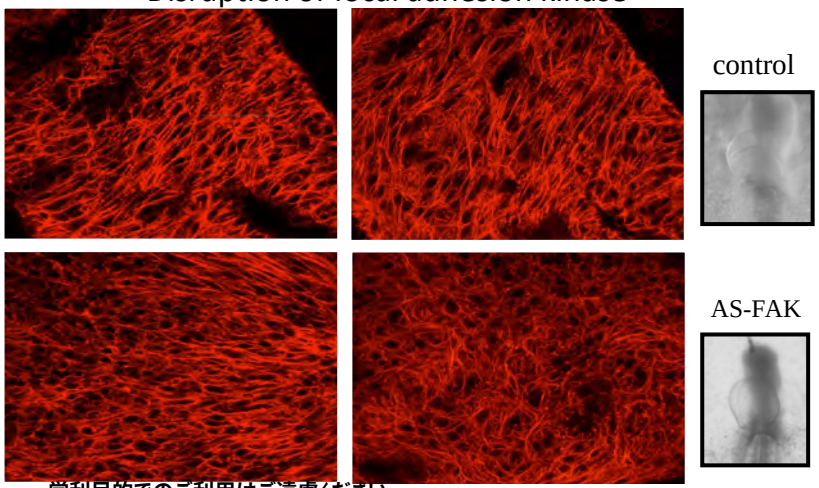
3-D observation of actin filaments during cardiac myofibrinogenesis in chick embryo using a confocal laser scanning microscope

Isao Shiraishi, Tetsuro Takamatsu, Tetsuhiro Minamikawa, and Setsuya Fujita



Anat Embryol 1992;185:401-8.

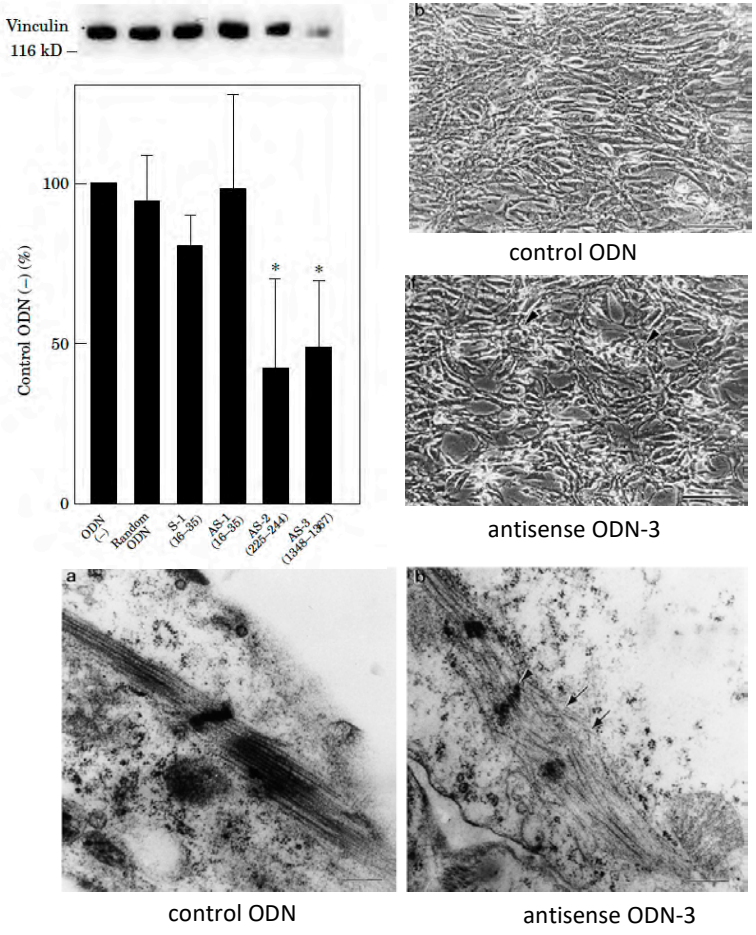
Disruption of focal adhesion kinase



Vinculin is an Essential Component for Normal Myofibrillar Arrangement in Fetal Mouse Cardiac Myocytes

Isao Shiraishi, David G. Simpson, Wayne Carver, Robert Price, Toshiro Hirozane, Louis Terracio and Thomas K. Borg

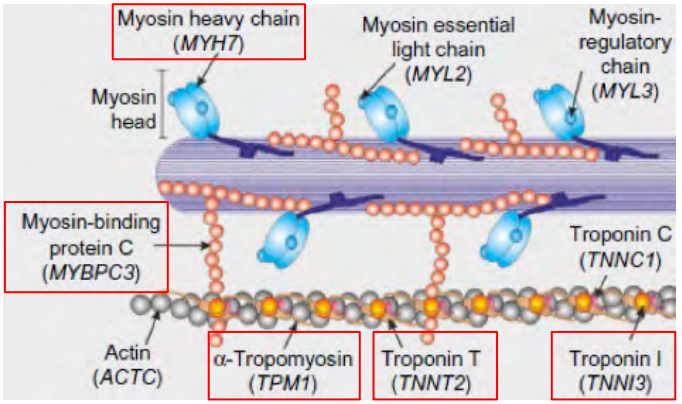
Department of Developmental Biology and Anatomy, School of Medicine, University of South Carolina, Columbia, SC 29208, USA

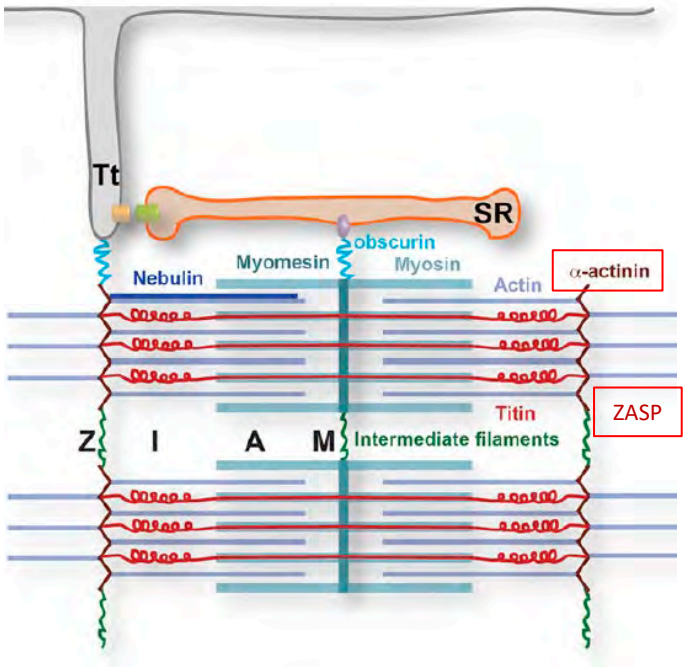


J Mol Cell Cardiol 1997;29:2041-2052.

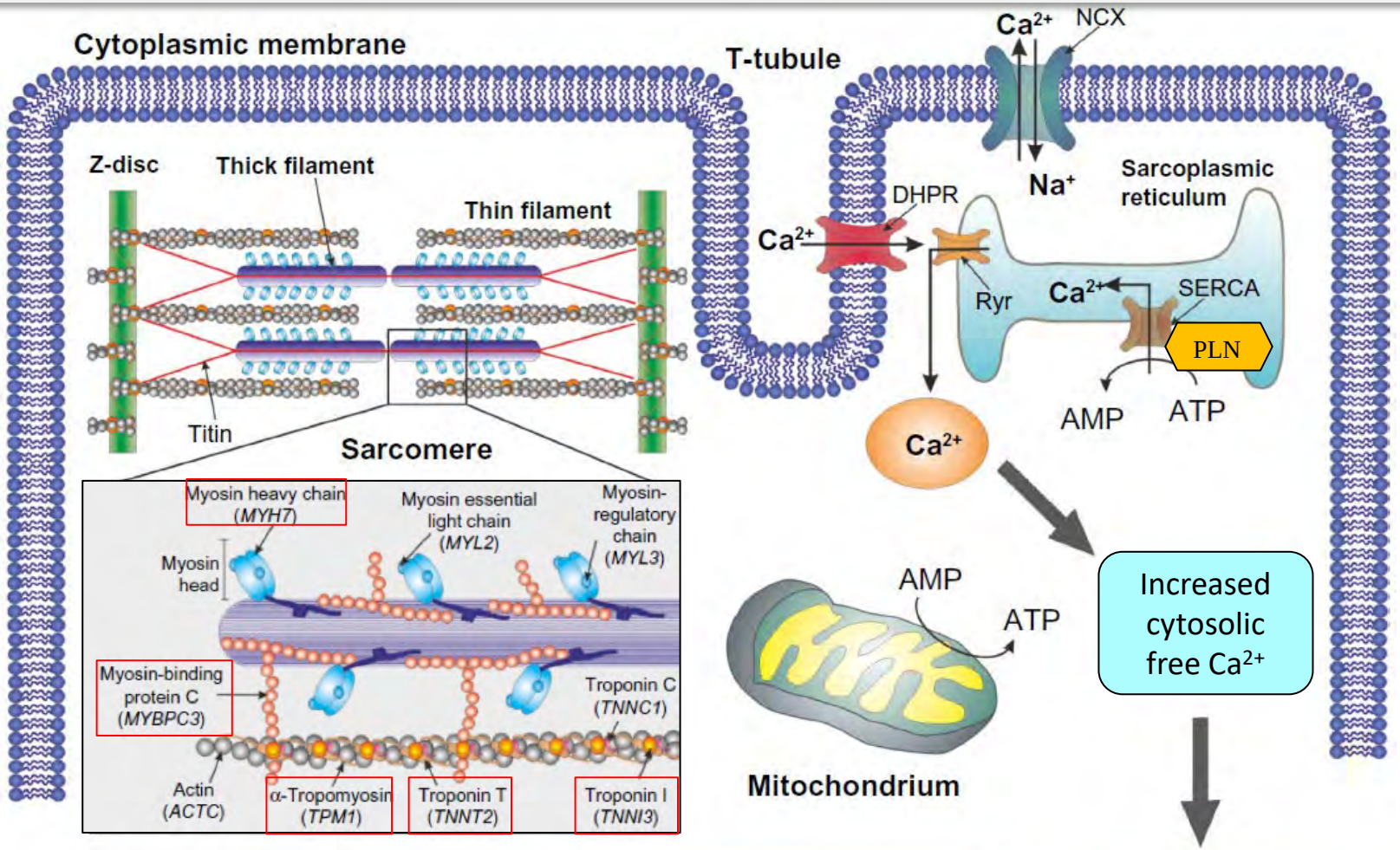
肥大型心筋症に見られる遺伝子異常

Hypertrophic cardiomyopathy			
Myofilament	MYBPC3	Cardiac myosin-binding protein C	15-25%
	MYH7	β-Myosin heavy chain	15-25%
	TNNI3	Cardiac troponin I	<5%
	TNNT2	Cardiac troponin T	<5%
	TPM1	α-Tropomyosin	<5%
	MYL2	Regulatory myosin light chain	<2%
	ACTC	α-Cardiac actin	<1%
	MYH6	α-Myosin heavy chain	<1%
	MYL3	Essential myosin light chain	<1%
	TNNC1	Cardiac troponin C	<1%
	TTN	Titin	<1%
Z-disk	LBD3	LIM-binding domain 3 (ZASP)	1-5%
	ACTN2	α-Actinin 2	<1%
	ANKRD1	Ankyrin repeat domain 1 (CARP)	<1%
	CSRP3	Muscle LIM protein	<1%
	VCL	Vinculin/metavinculin	<1%
Ca^{2+} handling	PLN	Phospholamban	<1%



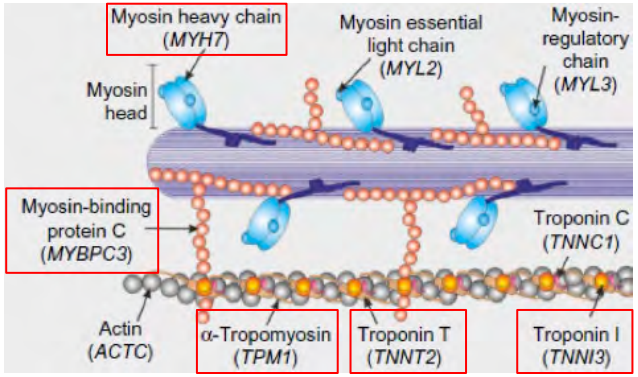


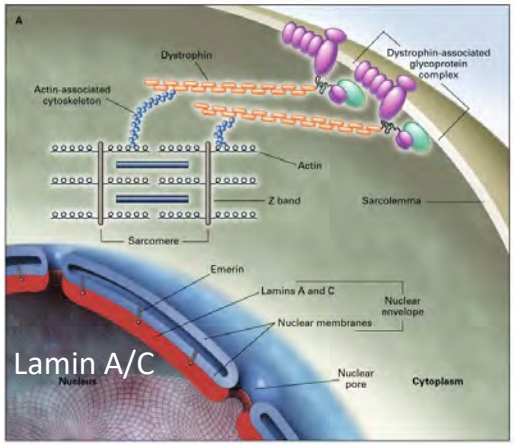
肥大型心筋症における心筋肥大の分子メカニズム

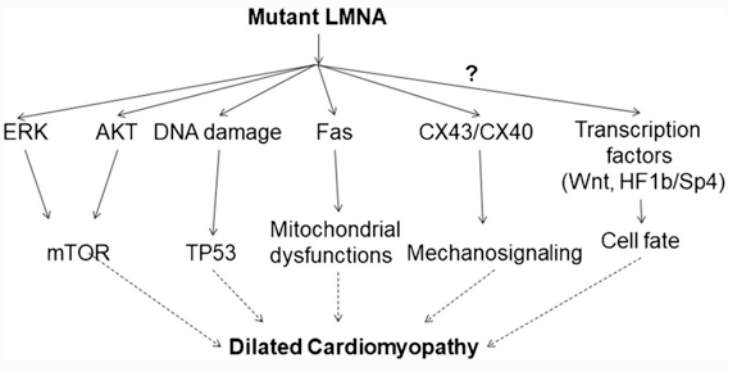


拡張型心筋症に見られる遺伝子異常

Dilated cardiomyopathy			
Sarcomere protein	TTN	Titin	25%
	MYH7	β-Myosin heavy chain	4%
	MYH6	α-Myosin heavy chain	4%
	MYBPC3	Cardiac myosin-binding protein C	2%
	TNNT2	Cardiac troponin T	3%
	TNNC1	Cardiac troponin C	<1%
	TNNI3	Cardiac troponin I	<1%
	TPM1	α-Tropomyosin	<1%
Z-disk protein	MYPN	Myopalladin	3%
Cytoskeleton	DES	Desmin	3%
	ZASP	LIM domain binding protein 3	1%
	VCL	Vinculin/metavinculin	1%
Nuclear membrane	LMNA	Lamin A/C	6%
Nuclear protein	RBM20	RNA-binding protein 20	2%
Ion channel	SCN5A	Sodium channel Type V	3%
SR protein	PLN	phospholamban	1%
Others	BAG3	Bcl2-associated athanogene 3	3%
	CRYAB	α-Crystalin B chain	1%



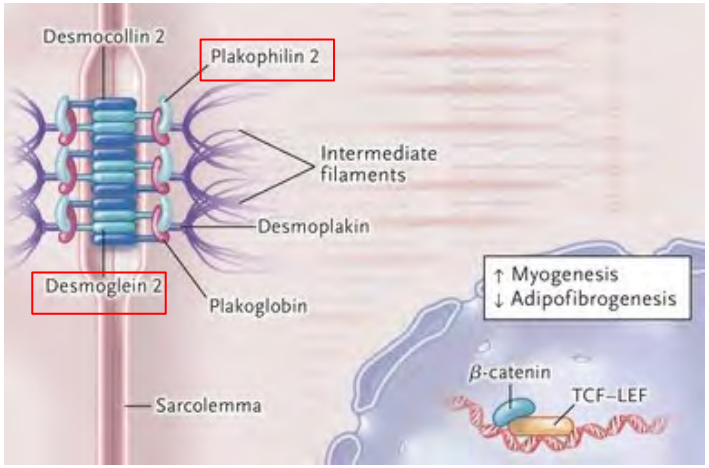


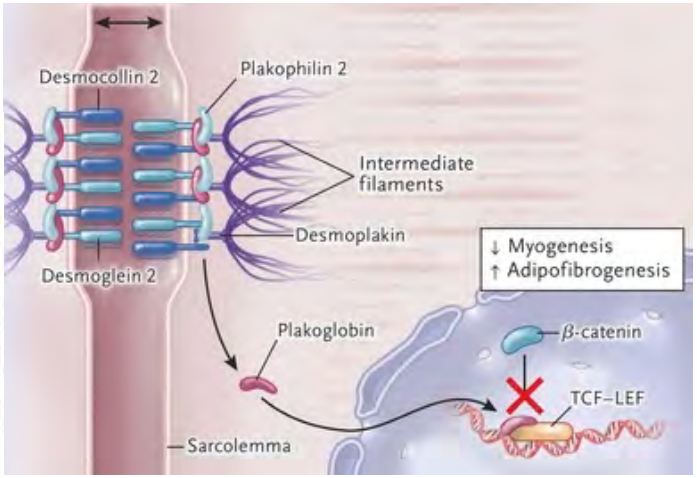


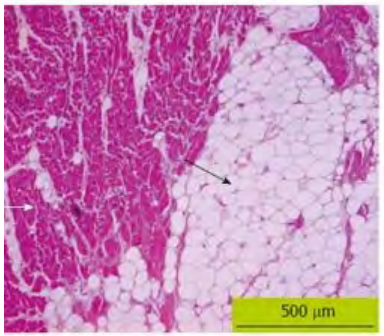
不整脈原性右室心筋症における遺伝子異常

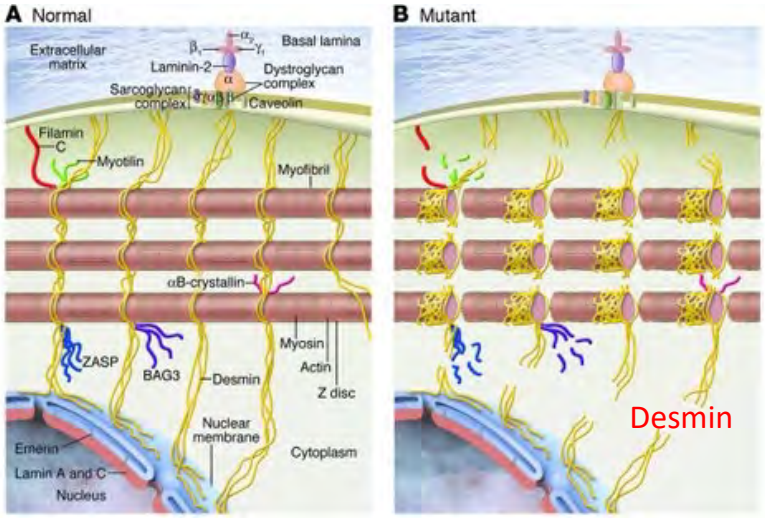
Arrhythmogenic right ventricular cardiomyopathy			
Desmosomal protein	PKP2	Plakophillin-2	11-43%
	DSG2	Desmoglein-2	12-40%
	DSP	Desmoplakin	6-16%
	DSC2	Desmocollin-2	rare
	JUP	Junctional plakoglobin	rare
Sarcomere protein	TTN	Titin	
Cytoskeletal protein	DES	Desmin	
Others	TGFB3	UTR of TGF-β	
	RYR2	Ryanodine receptor	

Desmosome and Desmin





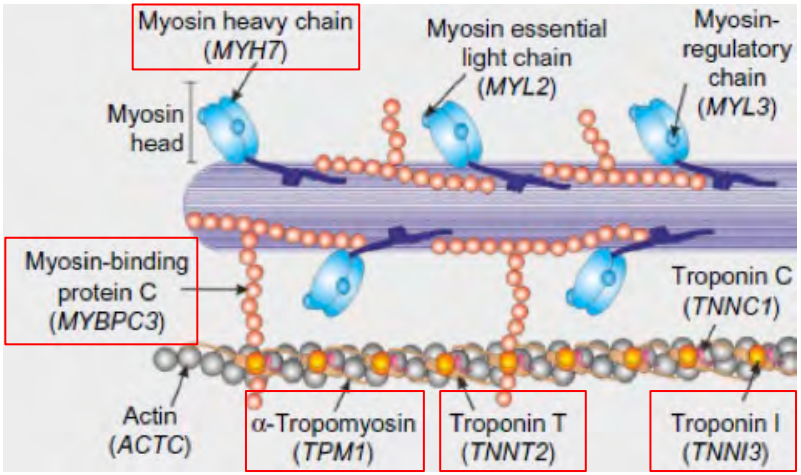


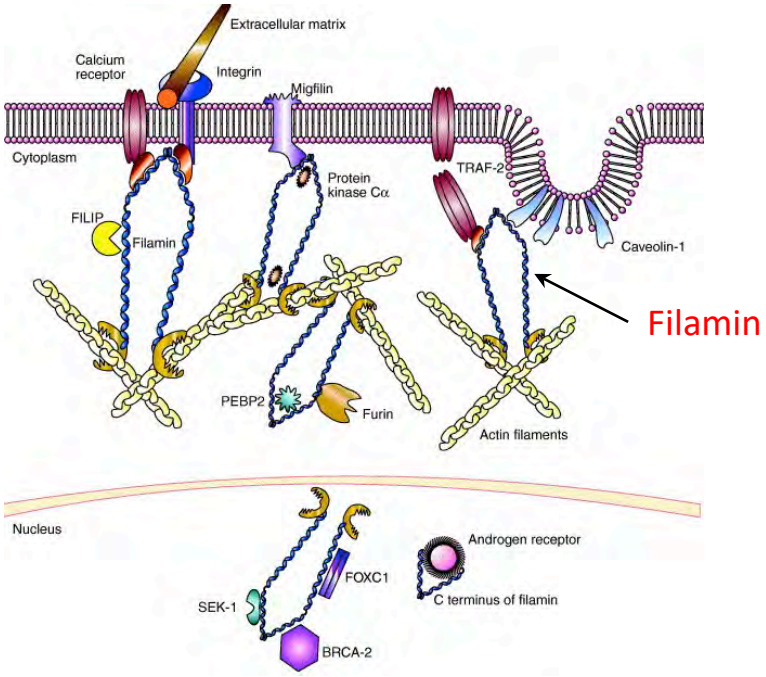


New Engl J Med 2017;376:61-72.

拘束型心筋症に見られる遺伝子異常

Restrictive cardiomyopathy			
Myofilament	MYBPC3	Cardiac myosin-binding protein C	N.A.
	MYH7	β-Myosin heavy chain	N.A.
	TNNI3	Cardiac troponin I	N.A.
	TNNT2	Cardiac troponin T	N.A.
	ACTC1	α-Cardiac actin	N.A.
	MYL3	Essential myosin light chain	N.A.
	FMN	Filamin C	N.A.
Nuclear membrane	LMNA	Lamin A/C	N.A.





遺伝子異常と表現型

Genetic background of Japanese patients with pediatric hypertrophic and restrictive cardiomyopathy

Takeharu Hayashi[1,2] · Kousuke Tanimoto[3] · Kayoko Hirayama-Yamada[1] · Etsuko Tsuda[4] · Mamoru Ayusawa[5] · Shinichi Nunoda[6] · Akira Hosaki[7] · Akinori Kimura[1]

Hayashi et al., J Hum Genet. 2018 Sep;63(9):989-996.

Hypertrophic cardiomyopathy (HCM) and restrictive cardiomyopathy (RCM) present a high risk for sudden cardiac death in pediatric patients. The aim of this study was to identify disease-associated genetic variants in Japanese patients with pediatric HCM and RCM. We analyzed 67 cardiomyopathy-associated genes in 46 HCM and 7 RCM patients diagnosed before 16 years of age using a next-generation sequencing system. We found that 78% of HCM and 71% of RCM patients carried disease-associated genetic variants. Disease-associated genetic variants were identified in 80% of HCM patients with a family history and in 77% of HCM patients with no apparent family history (NFH). *MYH7* and/or *MYBPC3* variants comprised 76% of HCM-associated variants, whereas troponin complex-encoding genes comprised 75% of the RCM-associated variants. In addition, 91% of HCM patients with implantable cardioverter-defibrillators and infant cases had NFH, and the 88% of HCM patients carrying disease-associated genetic variants were males who carried *MYH7* or *MYBPC3* variants. Moreover, two disease-associated *LAMP2*, one *DES* and one *FHOD3* variants, were identified in HCM patients. In this study, pediatric HCM and RCM patients were found to carry disease-associated genetic variants at a high rate. Most of the variants were in *MYH7* or *MYPBC3* for HCM and *TNNT2* or *TNNI3* for RCM.

53 patients age <16 : HCM (46) and RCM (7)

Analysis of 67 gene mutations using next-generation sequencing

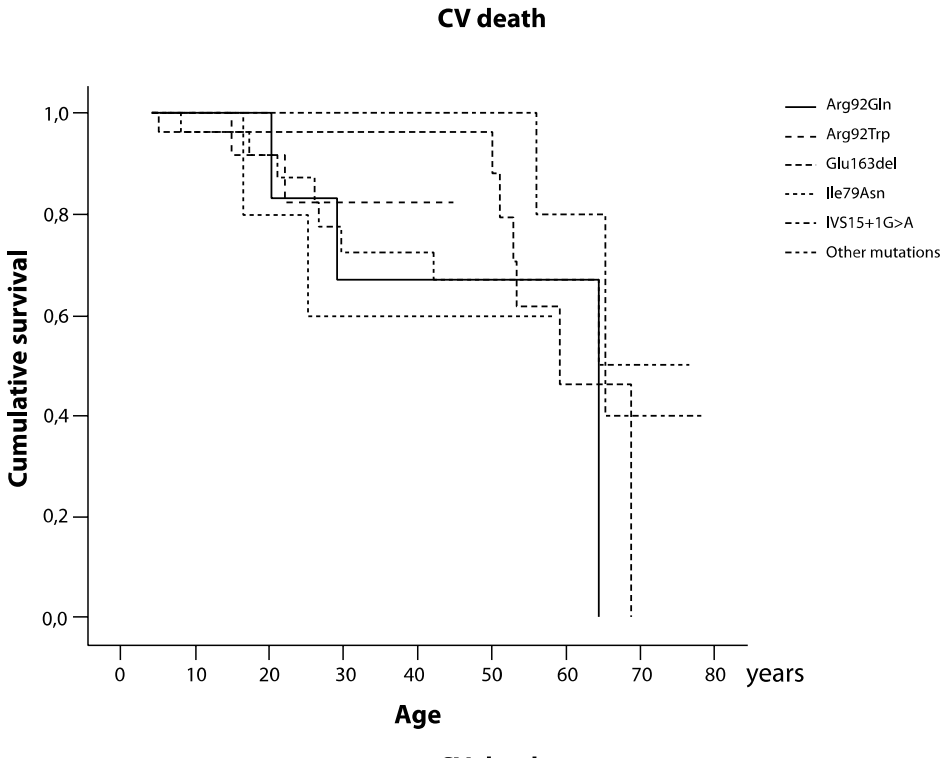
HCM 78% mutation (+) : MYH7 or MYBPC3 mutations in 76%

RCM 71% mutation (+) : TNNT2 or TNNI3 mutations in 75%

Long-Term Outcomes in Hypertrophic Cardiomyopathy Caused by Mutations in the Cardiac Troponin T Gene

Ferdinando Pasquale, MD, PhD; Petros Syrris, PhD; Juan Pablo Kaski, BSc, MBBS, MD; Jens Mogensen, MD, PhD; William J. McKenna, MD, DSc, FRCP, FESC; Perry Elliott, MD

Circ Cardiovasc Genet. 2012;5:10-17.



心筋症遺伝子異常への治療介入の可能性

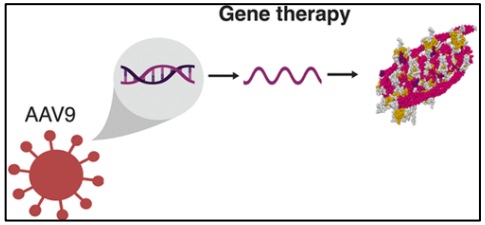
Novel Therapies for Prevention and Early Treatment of Cardiomyopathies
Now and in the Future

Giuliana G. Repetti, Christopher N. Toepfer, Jonathan G. Seidman, Christine E. Seidman

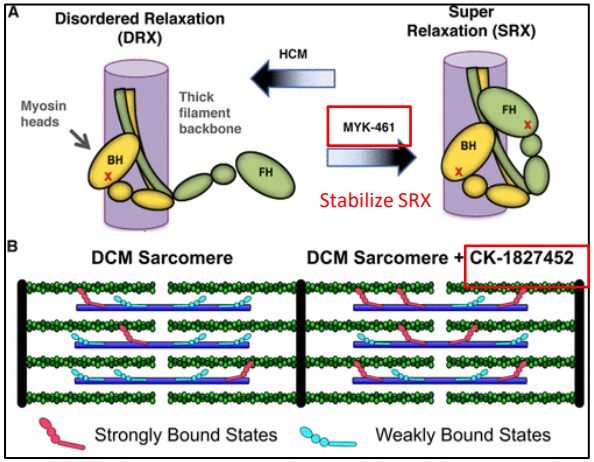
Abstract: **Heritable cardiomyopathies are a class of heart diseases caused by variations in a number of genetic loci. Genetic variants on one allele lead to either a degraded protein, which causes a haploinsufficiency of that protein, or a nonfunctioning protein that subverts the molecular system within which the protein works. Over years, both of these mechanisms eventually lead to diseased heart tissue and symptoms of a failing heart. Most cardiomyopathy treatments repurpose heart failure drugs to manage these symptoms and avoid adverse outcomes. There are few therapies that correct the underlying pathogenic genetic or molecular mechanism. This review will reflect on this unmet clinical need in genetic cardiomyopathies and consider a variety of therapies that address the mechanism of disease rather than patient symptoms. These therapies are genetic, targeting a defective gene or transcript, or ameliorating a genetic insufficiency. However, there are also a number of small molecules under exploration that modulate downstream faulty protein products affected in cardiomyopathies. (*Circ Res*. 2019;124:1536-1550. DOI: 10.1161/CIRCRESAHA.119.313569.)**

Circ Res 2019;124:1536-50.

Viral-mediated delivery of genes

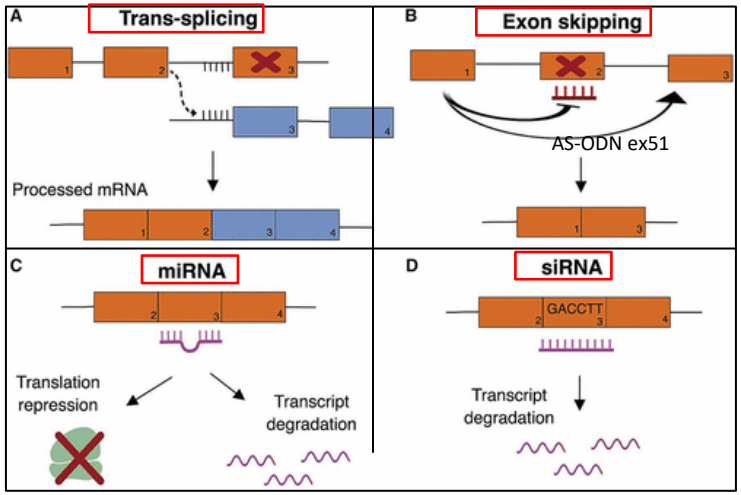


Small molecules to improve sarcomere



CK compound activates biomechanical cycle.

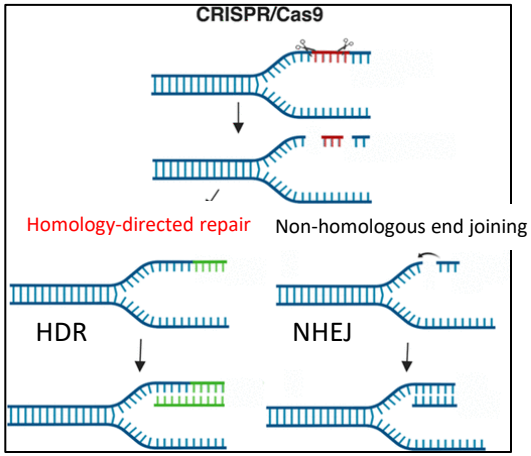
Strategies to correct aberrant transcripts



Partially sequence specific degradation

Sequence specific degradation

CRISPER/CAS9-mediated repair



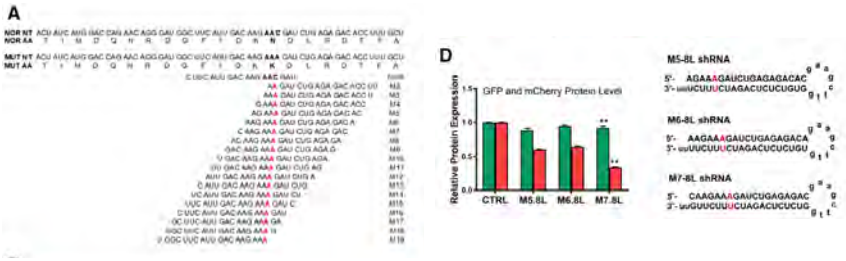
Sequence specific repair

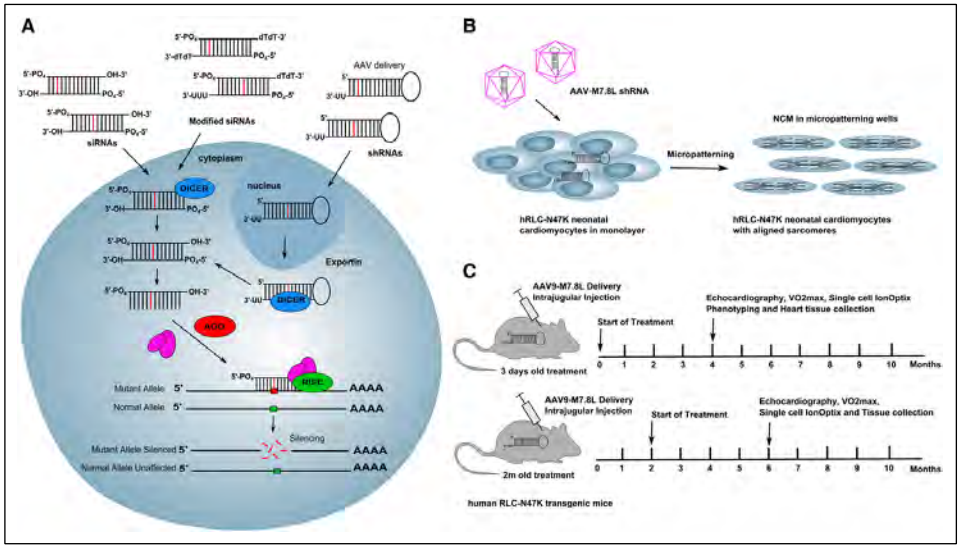
RNAi導入による拘束型心筋症マウスの治療の試み

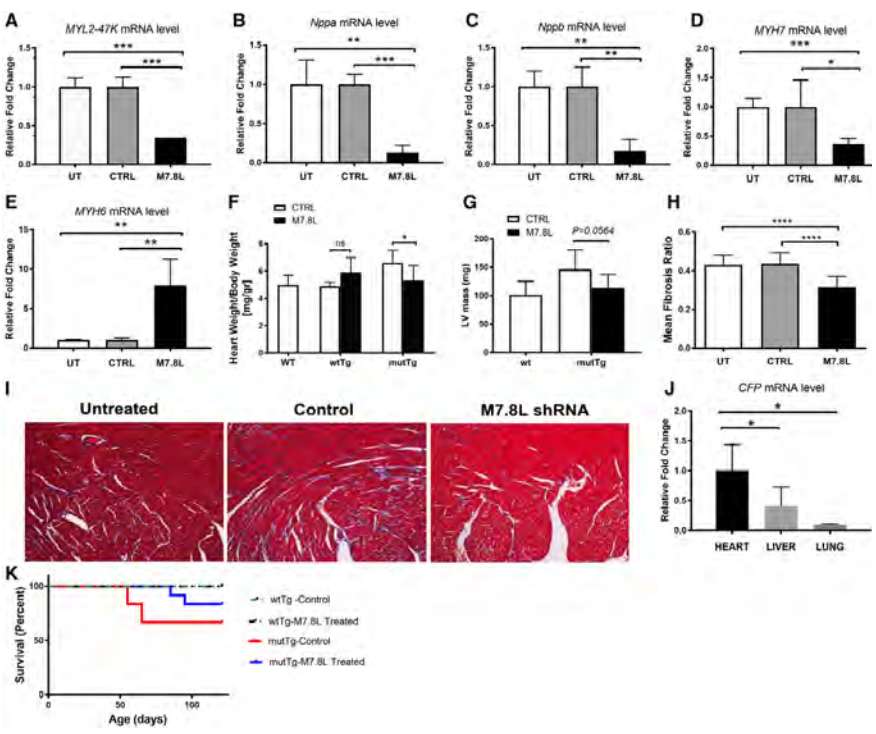
ORIGINAL RESEARCH ARTICLE

Allele-Specific Silencing Ameliorates Restrictive Cardiomyopathy Attributable to a Human Myosin Regulatory Light Chain Mutation

Zeleta-Rivera et al., Circulation 2019;140, 765-778.







- ✓ A short hairpin RNA (M7.8L) was selected from a pool for specificity and efficacy. Two groups of myosin regulatory light chain N47K transgenic mice were injected with M7.8L packaged in adeno-associated virus 9 at 3 days of age and 60 days of age .
- ✓ A one-time injection of AAV9-M7.8L RNAi in 3-day-old humanized regulatory light chain mutant transgenic mice silenced the mutated allele (RLC-47K) with minimal effects on the normal allele (RLC-47N) assayed at 16 weeks post injection.

まとめ

1. 多くの心筋症において遺伝子異常が明らかにされ、疾患の発症および病態の分子メカニズムが解明されるようになった。

2. 次世代シークエンサーの普及により、今後さらに心筋症の遺伝的異常は明らかにされることが予想される。

3. 今後は様々な遺伝子工学的アプローチを用いた、心筋症に対する高精度医療(precision medicine)による治療研究の発展が期待される。