Familial Dilated Cardiomyopathy

Clinical and Genetic Issues
in Familial Dilated Cardiomyopathy

College of Medicine, Chungbuk National University

Kyung-Kuk Hwang

Contents

- Definition (criteria)
- Clinical and family studies
  - Recognition of familial transmission
- Genetic studies
  - Disease gene and chromosomal loci
- Clinical screening recommendation
  - Family history and pedigree analysis
    Age-dependant penetrance and variable expression
- Genetic counseling and genetic testing

Dilated Cardiomyopathy (DCM)

- Idiopathic dilated cardiomyopathy (IDC)
  - 50% of DCM
  - diagnosis of exclusion : detectable causes should be excluded
    viral infection, excessive alcohol exposure, severe HT, autoimmune..

- Underlying genetic cause
  - mutation of genes : encoding key proteins in cardiovascular biology

Criteria for Familial DCM (FDC)

- One individual diagnosed with idiopathic DCM in a family, with at least:

  one relative also diagnosed with idiopathic DCM

  or

  one first-degree relative with

  an unexplained sudden death under the age of 35 years

  Mestroni L et al. *Eur Heart J*. 1999; 20: 93–102

- Presence of idopathic DCM in two or more family member

Cardiovascular Diseases Caused by Mutation

- Hypertrophic cardiomyopathy (HCM) : contractile protein
  Long QT syndrome
  Arrhythmogenic RV dysplsia
  Marfarn Syndrome

  Bicuspid aortic valve
  Atrial fibrillation

First Report

- N=104 IDC at Mayo clinic (1960-1973)
  by clinical and angiographic criteria
  F/U : 6 - 20 years

  The natural history of idiopathic dilated cardiomyopathy

- 21 % : excessive consumption of alcohol
  20 % : severe influenza-like syndrome within 60 days
  before the appearance of cardiac manifestations
  8 % : rheumatic fever

  2 % (n=2) : *familial aggregation*

Fuster B et al. Am J Cardiol 1981;47:525–31.

Clinical and Family Studies to Assess Frequency of Familial Dilated Cardiomyopathy

Author and Year	Location of Study	Patient Population	Method to Identify Familial Disease	Number of FDC/ Number of IDC (%)
Fuster, 1981	Rochester, MN	Consecutive IDC patients diagnosed 1960–1973, Mayo Clinic	Retrospective chart review of available history	2 of 104 (2%)
Lengyel, 1981	Budapest, Hungary	All patients studied with echocardiography and IDC, 1973–1979, Hungarian Institute of Cardiology	Not stated	5 of 98 (5%)
Michels, 1985	Rochester, MN	Patients <50 yrs with IDC, 1976–1982, Mayo Clinic	Retrospective chart review, prospective family history screening questionnaire	11 of 165 (7%)
Pongpanich, 1986	Bangkok, Thailand	Consecutive pediatric patients with congestive cardiomyopathy, 1969–1984, Mahidol University	Family history of sibling with same condition	5 of 50 (10%)
Fragola, 1988	Rome, Italy	12 of 43 patients with IDC in 1985–1986 consented to participate, none with positive FH, University of Rome	Prospective echocardiographic screening	4 of 12 (33%)
Griffin, 1988	St. Louis, MO	Children diagnosed with IDC 1975–1985, Washington University	Telephone follow-up; group I <2 yrs of age at presentation, group II >2 yrs of age at presentation	Group I: 0 of 20 (0%); group II: 3 of 12 (25%)
Valantine, 1989	Stanford, CA	All cardiac transplant recipients 1976–1986, Stanford University	Retrospective history review	11 of 179 (6%)
Keren, 1990	Jerusalem, Israel; Stanford, CA	Patients with mildly dilated cardiomyopathy, Hadassah and Stanford universities	Not stated	9 of 16 (56%)
Mestroni, 1990	Trieste, Italy	Consecutive patients with IDC, 1979–1988, University of Trieste	Prospective historical screening	12 of 65 (7%)
Michels, 1992	Rochester, MN	Patients with ejection fraction <50% and IDC identified by medical record review, 1987–1989, Mayo Clinic	Prospective echocardiographic screening of relatives of patients with IDC	12 of 59 (20%)

Burkett EL et al, J Am Coll Cardiol 2005;45:969-81

Clinical and Family Studies to Assess Frequency of Familial Dilated Cardiomyopathy

Author and Year	Location of Study	Patient Population	Method to Identify Familial Disease	Number of FDC/ Number of IDC (%)
Zachara, 1993	Rome, Italy	Consecutive patients with diagnosis of IDC	Retrospective historical screening for FDC	12 of 105 (11%)
Keeling, 1995	London, England	Prospectively identified cases of IDC at St. Georges Hospital	Prospective echocardiographic screening of first degree relatives	10 of 40 (25%)
Honda, 1995	Kobe, Japan	Patients with IDC 1973–1990 at Kobe University Hospital	Prospective evaluation of relatives	10 of 117 confirmed (9%), 29 of 117 suspected (25%)
Goerss, 1995	Rochester, MN	59 IDC patients from 1992 Michels report and 36 new IDC patients, Mayo Clinic	Prospective echocardiographic screening of relatives of patients with IDC	23 of 95 (24%), (27 of 95 indeterminate)
McKenna, 1997	Dublin, Ireland	Patients with IDC with family members and who participated in FDC screening, University College	Prospective echocardiographic screening of first degree relatives	14 of 56 (25%) definite, 15 of 56 (27%) possible
Grünig, 1998	Heidelberg, Germany	Consecutive patients with IDC 1988–1994, University of Heidelberg	Prospective family history and clinical screening in some (see text)	156 of 445 (35%)
Baig, 1998	London, England	Consecutive patients with IDC at St. Georges Hospital	Prospective clinical and echocardiographic screening of relatives	52 of 110 (48%) when LVE included
Mestroni, 1999	Trieste, Italy	Consecutive patients referred to the International Centre for Genetic Engineering and Biotechnology, 1991–1997; 60 of 350 patients screened based on feasibility	Prospective clinical and echocardiographic screening of relatives	39 of 60 (65%)
Michels, 2003	Rochester, MN	Patients with IDC who participated in earlier family studies (Michels 1992, Goerss 1995) at Mayo Clinic	Family follow-up study	30 of 101 (30%)

Burkett EL et al, J Am Coll Cardiol 2005;45:969-81

FDC in an Outpatient Heart Failure Clinic

- IDC or FDC in outpatient clinic data

  N= 116, M= 78 (67%), age: 51±13 yrs,
  NYHA ≥ II : 69%, sinus rhythm: 87%, LBBB: 34 %
  LVEF in the last EchoCG : 38±12%, LVED Dimension: 62±8 mm.

- Mean F/U: 3.7±5.0 yrs, IDC etiology was change in 33 (28%)

- Hereditary cause in 52 (45%) patients,
  documenting relatives with IDC in 41 cases (79%)
  sudden death before the age of 35 in 6 (12%)
  IDC and sudden death in 5 (10%)

In 28 different families, 6 individuals with asymptomatic IDC.
  age at the first sx : 40±14 yrs
  EchoCG on first consult: LVEF = 29±10%, LVEDD:56±10 mm

Martins E et al, Heart failure clinic abstract 2007

Natural History of FDC

- N= 441, DCM in Heart Muscle Disease Registry of Trieste (1978-1997)

  Prospective F/U: 81±50 months
  Extensive pedigree evaluation and, when available, molecular genetic study

  FDC : 19% at enrollment

- FDC vs IDC

  More younger (39±14 vs 47±14 yrs, p<0.0001)
  less HF symptoms (44 vs 67%, p<0.0001), less LBBB (18 vs 35%, p=0.0002)
  LV EF (32±10 vs 31±11%, p=NS), LVEDD (37±6 vs 38±7 mm/m2, p=NS)

  2, 4, 8-yr transplant-free survival : 91, 88, 79% vs 89, 78 and 64% (p=0.011)
  2, 4, 8-yr hospitalization-free survival : 68, 65, 50% vs 69, 54, 37% (p=0.041).

  Pts with FDC show a better long-term outcome

- ? Effect of early detection

Lenarda AD et al, J Am Coll Cardiol abstract 2002

Clinical Issues of FDC

- Familial inheritance : 20-50% of IDC cases
- Several issues may compound identification of FDC

  - age-dependent and variable penetrance

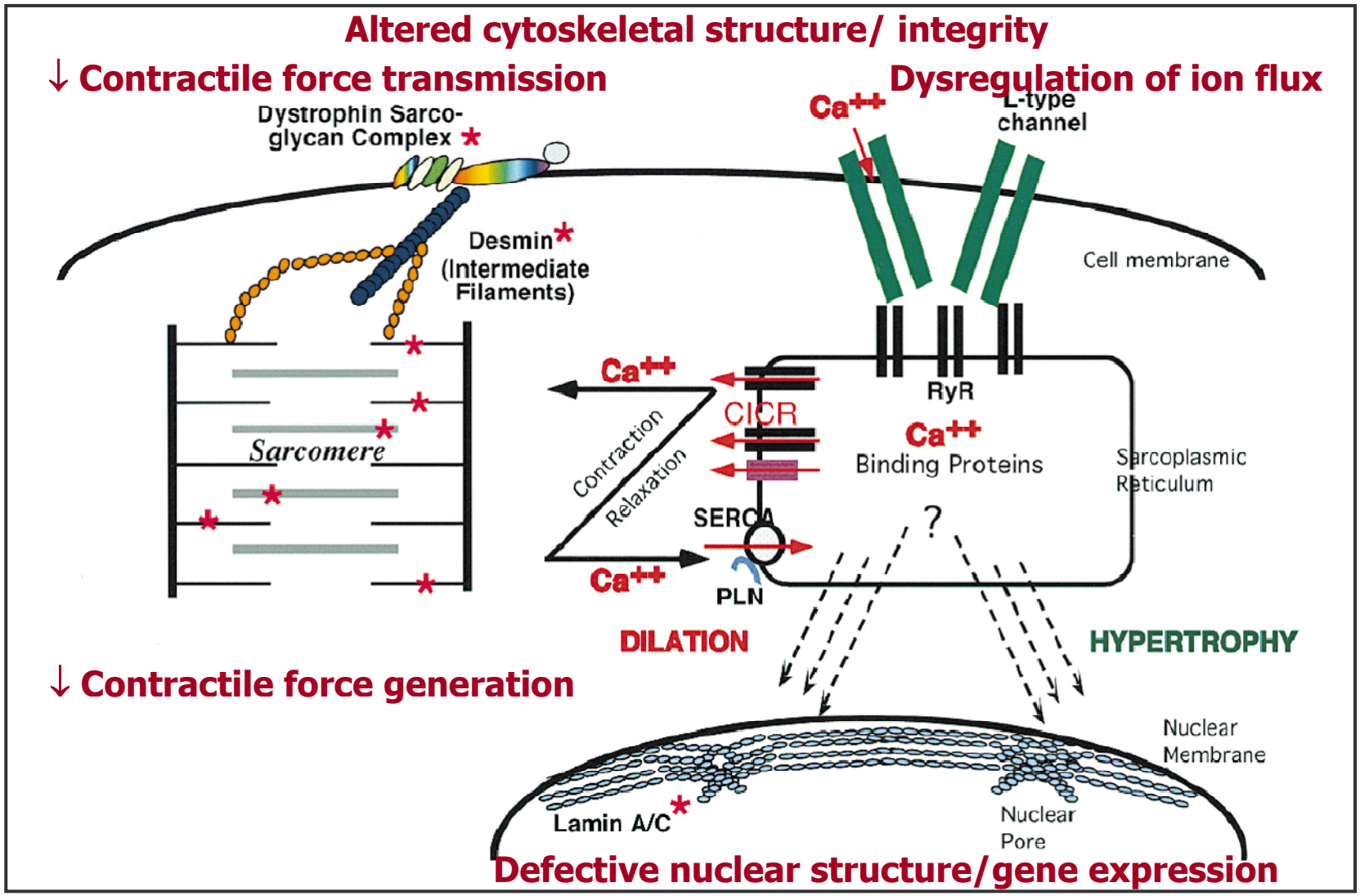
    : phenotype ; from the third to sixth decade or even later
    variable clinical presentation and disease progression
    clinically evident disease may not be present in family members simultaneously

  - no unique clinical features to IDC or FDC

    : HF, sudden cardiac death, arrhythmias

  - comprehensive family history may be thwarted

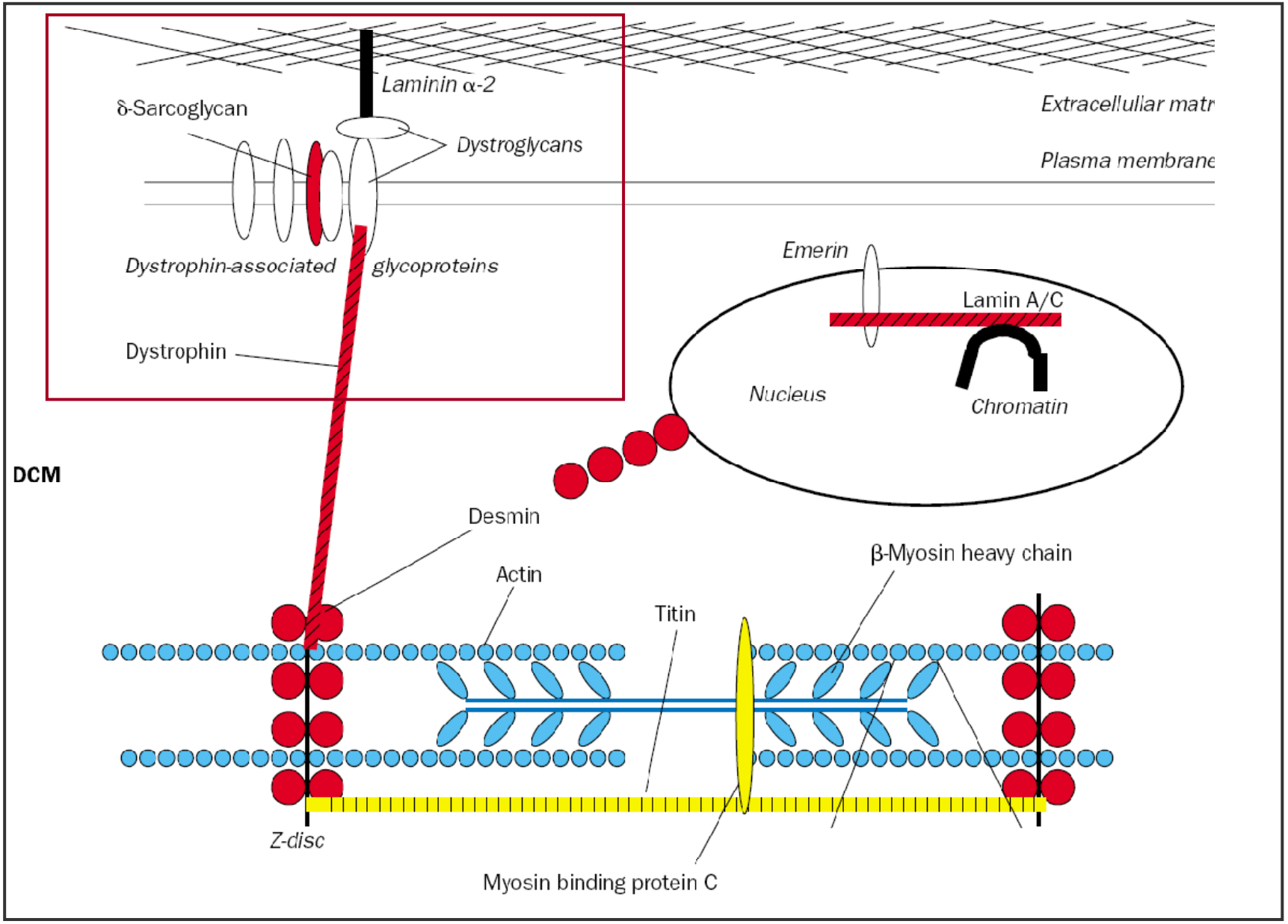
FDC Disease Genes



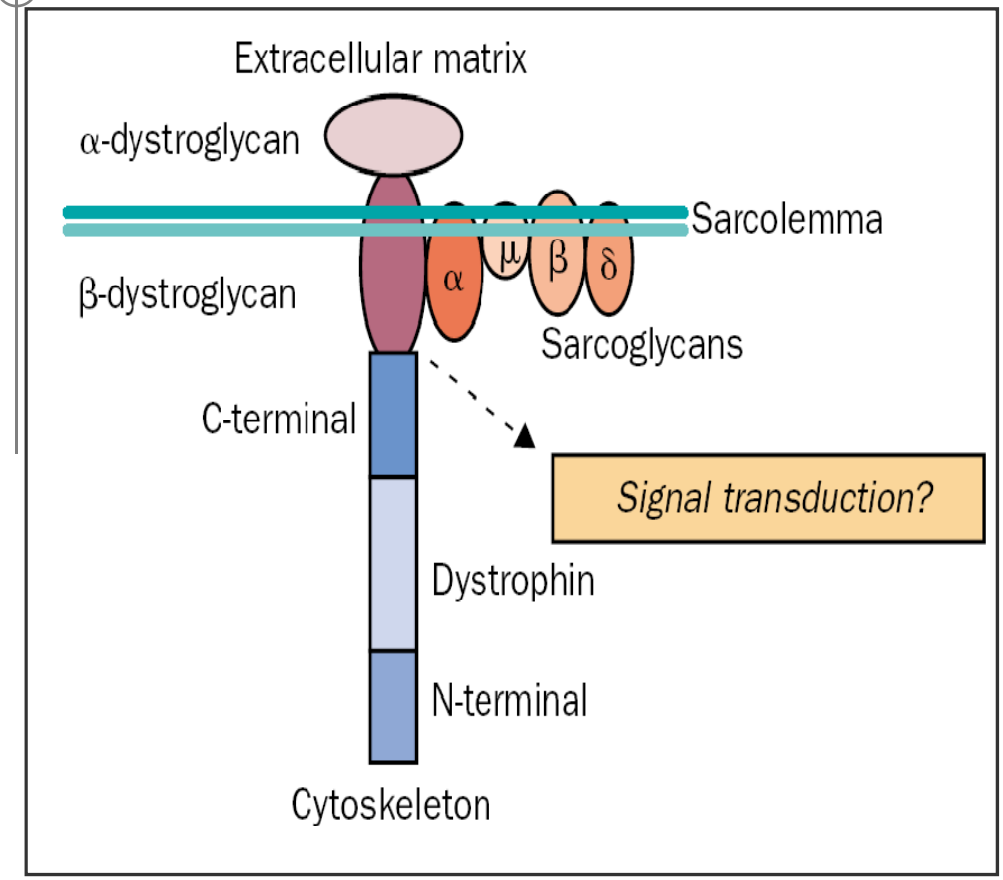
Seidman JG et al Cell. 2001:104:557-567
Menon SC et al, Progress in Pediatric Cardiology 2008:25:57–67

Postulated Mechanisms of FDC

- Decreased force generation
  - Cardiac actin, ®−Myosin heavy chain, Cardiac troponin T
  - α-Tropomyosin, Myosin-binding protein C, α-Myosin heavy chain
- Disordered force transduction
  - Dystrophin, Desmin, y-Sarcoglycan, α-Actinin-2
  - ? Titin
- Altered cytoskeleton assembly
  - Titin, Metavinculin, Cypher/LIM binding domain 3
- Altered calcium signaling
  - Phospholamban
- Altered K+ channels
  - SUR2A
- Disordered gene expression
  - ? Lamin A/C
- Nuclear fragility/apoptosis/myocyte loss
  - ? Lamin A/C


Laminin α-2
δ-Sarcoglycan
Extracellular matr
Dystroglycans
Plasma membrane
Dystrophin-associated
glycoproteins
Dystrophin
Emerin
Lamin A/C
Nucleus
Chromatin
DCM
Desmin
Actin
β-Myosin heavy chain
Titin
Z-disc
Myosin binding protein C

Dystrophin-associated protein complex



Deficiencies of dystrophin or sarcoglycans

↓

congenital dilated cardiomyopathy

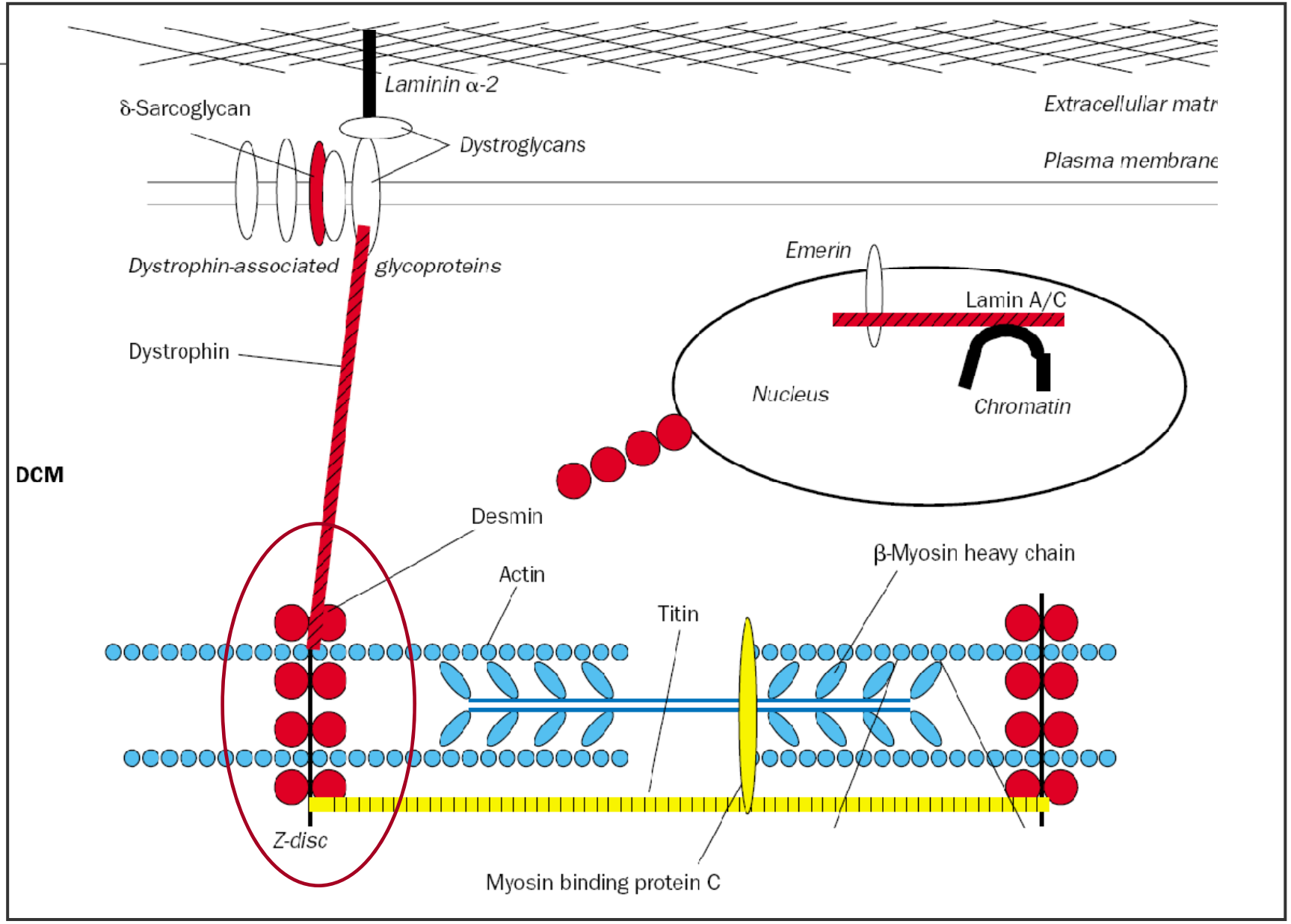
Cleavage of dystrophin by protease 2A

↓

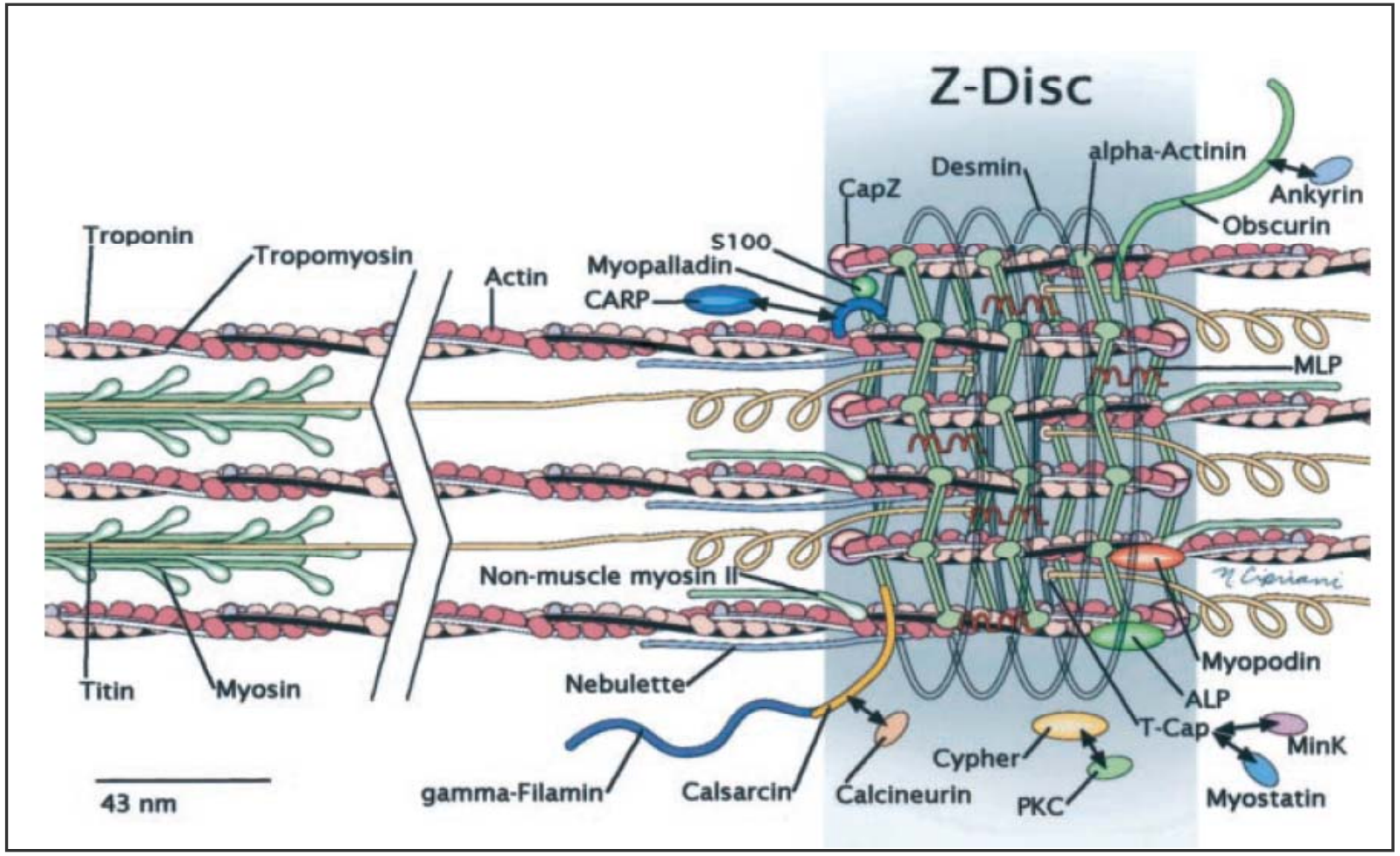
viral dilated cardiomyopathy

- Linkage of ECM to cytoskeleton : mechanical stability for sarcolemma to resist contractile and osmotic stresses.
- Signal-transduction module, linking mechanical stresses in sarcolemma to protein kinase pathways.

Ganote CE et al Lancet. 2002:259:905-6


Laminin α-2
δ-Sarcoglycan
Extracellular matr
Dystroglycans
Plasma membrane
Dystrophin-associated glycoproteins
Emerin
Lamin A/C
Dystrophin
Nucleus
Chromatin
DCM
Desmin
Actin
β-Myosin heavy chain
Titin
Z-disc
Myosin binding protein C

Z-Discs in Intracellular Signaling



Critical element in regulation of myocardial function by changes in cell stress and strain

Pyle WG et al Cir Res. 2004:94:286-305

- over 20 genes and 30 chromosomal loci have been implicated in the pathogenesis of DCM

Dilated Cardiomyopathy Genes/Loci

Locus	Inheritance	Gene	Mechanism	Protein	Protein class	Other features
1p1–q21	AD	*LMNA*	4	Lamin A/C	Inner nuclear membrane	Conduction disease, SND, AF, +/− skeletal myopathy, and conduction system disease
1q31–q42	AD	*PSEN2*	5	Presenilin 2	Calcium signaling	Ventricular septal defect and bicuspid aortic valve and Alzheimer disease
1q32	AD	*TNNT2*	3	Cardiac troponin T	Thin filament of sarcomere	None
1q42–q43	AD	*ACTN2*	1	Actinin, alpha 2	Z-disc, intercalated disc	None
2q14–q22	AD	?	?	?	?	Conduction disease
2q31	AD	*TTN*	1	Titin	Sarcomeric cytoskeleton	None
2q35	AD	*DES*	1	Desmin	Extra-sarcomeric cytoskeleton	Skeletal myopathy
3p21	AD	*TNNC1*	3	Cardiac troponin C	Thin filament of sarcomere	HCM
3p22–p25	AD	*SCN5A*	5	Cardiac sodium channel alpha subunit	Voltage-gated ion channel	Conduction disease, sinus node dysfunction, AF
4q11	AD	*SGCB*	1	Beta sarcoglycan	Membrane-associated cytoskeleton	None
5q33–34	AD	*SGCD*	1	Delta sarcoglycan	Membrane-associated cytoskeleton	Skeletal myopathy
6p23–p4	AD	*DSP*	1	Desmoplakin	Membrane-associated cytoskeleton	Woolly hair, keratoderma, recessive transmission, ARVD
6q12–q16	AD	?		?	?	None
6q22.1	AD	*PLN*	5	Phospholamban	Sarcoplasmic reticulum	None
6q23–q24	AD	*EYA4*	4	Eyes absent homolog 4	Transcriptional coactivator	Skeletal myopathy, sensorineural hearing loss
9q13–q22	AD	?	?	?	?	None
9q22–q31	AD	?	?	?	?	None
10q22–q23	AD	*VCL*	1	Metavinculin	Intercalated disc	Mitral valve prolapse
10q22.3–q23.2	AD	*ZASP/LBD3*	1	LIM domain binding 3	Z-disc	Left ventricular noncompaction
11p11.2	AD	*MYBPC3*	3	Myosin-binding protein C, cardiac	Sarcomeric cytoskeleton	None
11p15.1	AD	*CSRP3*	1	Cardiac muscle LIM protein (MLP)	Z-disc	None
12p12.1	AD	*ABCC9*	6	Sulfonyl urea receptor 2A (SUR2A)	ATP-sensitive ion channel	Ventricular arrhythmias
12q22	AD	*TMPO*	4	Thymopoietin	Nuclear membrane	None
14q12	AD	*MYH6*	3	Cardiac alpha-myosin heavy chain	Thick filament of sarcomere	None
14q12	AD	*MYH7*	3	Cardiac beta-myosin heavy chain	Thick filament of sarcomere	None
14q24.3	AD	*PSN1*	5	Presenilin 1	Calcium signaling	Alzheimer disease
15q14	AD	*ACTC1*	2	Cardiac actin	Thin filament of sarcomere	None
15q22	AD	*TPM1*	2	Alpha-tropomyosin 1	Thin filament of sarcomere	None
16p11	AD	*CTF1*	?	Cardiotrophin 1	Cytokine	None
17q21	AR	*JUP*	1	Junctional plakoglobin	Membrane-associated cytoskeleton	ARVD, wooly hair and keratoderma
17q12	AD	*TCAP*	1	Tinin-Cap (teletonin)	Z-disc	None
19q13.42	AR	*TNNI3*	3	Troponin I, cardiac	Thin filament of sarcomere	None
Xp21	X-linked	*DMD*	1	Dystrophin	Membrane-associated cytoskeleton	Skeletal myopathy, subclinical myopathy, CK elevation
Xq28	X-linked	*TAZ(G4.5)*	1	Tafazzin	?	Skeletal myopathy, short stature, neutropenia
Mitochondrial	mtDNA	many	6	Respiratory chain protein or tRNA	Energy production	Skeletal myopathy, Lactic acidosis, other organ disease

Menon SC et al, Progress in Pediatric Cardiology 2008:25:57–67

Autosomal Dominant FDC, DCM Phenotype	Protein	Function	Disease Presentation /Characteristics
ACTC	Cardiac actin	sarcomeric protein; muscle contraction	MM in 2 unrelated families.
DES	Desmin	dystrophin-associated glycoprotein complex; transduces contractile forces	MM, 1 family, 2 affected, 2 unaffected. Other deceased family members died between 15-37 yrs of HF
SGCD	δ-sarcoglycan	dystrophin-associated glycoprotein complex; transduces contractile forces	MM in 1 family, onset of HF/SCD from 14-38 yrs; 2 IDCs with HF at 9 months and 14 yrs.
MYH7	β-myosin heavy chain	sarcomeric protein; muscle contraction	MMs in 2 of 20 families. Family 1: age at diagnosis 2-57 yrs, 6 of 19 < 20 yrs at diagnosis; aggressive disease, HF, SCD. Family 2: 4 with very early onset (at birth, 2 and 11 yrs; 1 SCD at 2 months). 2 MMs in 46 pts with IDC (mean age of IDC onset 29years)
TNNT2	Cardiac troponin T	sarcomeric protein; muscle contraction	2 unrelated families, same 3 bp deletion; early-onset DCM (of 14 affected, 2 infants, 3 teens, and 4 in 20s), prominent SCD. 1 family, MM in 20; 14 affected, highly variable severity (HF, death in 2-yr-old, to minor symptoms later). 1 family, same 3 bp deletion), highly variable age of onset of HF.
TPM1	α-tropomyosin	sarcomeric protein; muscle contraction	MMs, 2 pts with FDC (of 350 unrelated pts with IDC/FDC). Family 1: onset at 26 yrs with NSVT; subsequent death while awaiting transplant. Family 2: onset at 3 months, transplanted at 10 years; mother with IDC

Burkett EL et al, J Am Coll Cardiol 2005;45:969-81

Autosomal Dominant FDC, DCM Phenotype	Protein	Function	Disease Presentation /Characteristics
TTN	titin	sarcomere structure/extensible scaffold for other proteins	1 MM, 1 NM, 2 large families. 1 family with LVE in teens. DCM, HF: transplant in 3rd-6th decades.
VCL	metavinculin	sarcomeric structure; Intercalated disc	3 bp deletion in a 39-year-old man with IDC; MM, 52-yr-old woman, 2 affected relatives.
MYBPC	myosin-binding protein C	sarcomeric protein; muscle contraction	MM in 1 of 46 young pts with IDC.
MLP/CSRP3	muscle LIM protein	sarcomere stretch sensor/Z discs	W4R mutation in 9 German pts (three families) from a cohort of 536 German pts with IDC: 0 of 136 Japanese IDC pts had W4R mutation.
ACTN2	α-actinin-2	sarcomere structure; anchor for myofibrillar actin	MM in proband with DCM, died at 7 yrs; father died of IDC at 42 yrs (no DNA).
PLN	phospholamban	sarcoplasmic reticulum Ca^{++} regulator; inhibits SECA2 pump	NM, 1 family (of 20 screened) with aggressive, early-onset DCM, HF in 3rd decade; 4 of 12 transplanted. 2 Greek families with same NM (from 76 unrelated pts screened), with DCM in 3rd decade in homozygous NM carriers; variable onset.
ZASP/LBD3	Cypher/LIM binding domain 3	cytoskeletal assembly; involved in targeting and clustering of membrane proteins	From a cohort of 100 unrelated individuals with DCM (15 with isolated noncompaction of LV myocardium, or INLVM), mutations identified in 6 pts, 2 (1 INLVM) FDC and 4 IDC (3 INLVM). Wide range of age of onset, from infancy to 2nd to 5th decades.
MYH6	α-myosin heavy chain	sarcomeric protein; muscle contraction	Preliminary report of 3 MMs from 66 FDC families
ABCC	SUR2A	regulatory subunit of Kir6.2, an inwardly rectifying cardiac KATP channel	1 insertion/deletion mutation, 1 MM in 2 of 323 subjects with IDC. Age at diagnosis 40 and 55 yrs. Both with DCM, HF, ventricular tachycardia.

Burkett EL et al, J Am Coll Cardiol 2005;45:969-81

Autosomal Dominant FDC, DCM Phenotype	Protein	Function	Disease Presentation/Characteristics
LMNA	lamin A/C	xinner leaflet, nuclear membrane protein; confers stability to Nuclear membrane; gene expression	MMs in 5 of 11 families (39 total affected) with DCM and CSD. Disease onset mean 38 yrs (range 19-53 yrs) with asymptomatic ECG changes in rate/rhythm, then progressive sinus/AV node dysfunction, 1st, 2nd, 3rd degree heart block; 50% had Af or AF, 50% required pacemakers 65% with DCM (mild LV dysfunc tion in 12, HF in 13); 6 transplants, 11 SCD; no MD. 1 family, 5 affected (4-30 yrs), 3 with MD, mildly increased CK. 2 large families with CSD progressive to DCM, HF, transplant, or SCD. Family 1: 11 affected of 18 MM, mean disease onset at 43 yrs. Family 2: 12 affected of 14 NM, mean disease onset at 31 yrs. No MD. Other reports with prominent CSD, age of onset usually 30-50 yrs, some HF, occasional MD. 4 MMs after screening 40 FDC and 9 IDC DNAs.
X-linked FDC	**Protein**	**Function**	**Disease Presentation/ Characteristics**
DMD	dystrophin	primary component of Dystrophin-associated Glycoprotein complex: Transduce contrctile protein	Males present at 20-40 yrs and have rapid disease progression; carrier females may be affected with a milder phenotype. May have skeletal myopathy. Creatine kinase levels may be increased.
TAZ/G4.5	tafazzin	unknown	Infantile, lethal dilated cardiomyopathy.
Recessive FDC	**Protein**	**Function**	**Disease Presentation/ Characteristics**
TNN13	cardiac troponin I	sarcomeric protein, muscle contraction	One nuclear family, 2 homozygous siblings with DCM, and 1 sibling and parents who were heterozygous and had normal cardiovascular evaluations.

MM=missense mutation; NM=nonsense mutation;

Burkett EL et al, J Am Coll Cardiol 2005;45:969-81

Clinical Genetics of FDC

- Establishing causality of DCM from gene mutation
  - In case of AD : single base missense or nonsense mutation
  - Disease phenotype : segregate with mutation in a large family
    identified in multiple family
  - DCM in and animal model of gene mutation

- Pentrance and disease expression
  - Penetrance: measure of the percentage of individuals who carry a particular gene mutation who affected by the disorder
  - FDC: incomplete age-dependent pentrance
    variable expression

Clinical Genetics of FDC

- Particular gene mutation

  - wide variability in phenotypic effects and severity, both within and between families

  - wide range of mild to severe dis. across all generations

- Within the same family,
  - from subtle clinical symptoms, mild arrhythmias to sudden death or DCM leading to HF and/or cardiac transplantation.

- Family pedigrees as a single genetic entity: difficult to recognize FDC

- Genetic counseling
  - adult with mild or non-penetrant disease
    : risk for having offspring with a more severe phenotype.

Clinical Screening Recommendation for FDC

Family history and pedigree analysis

- three-generation pedigree : obvious history of DCM or HF
- goal of pedigree analysis
  : diagnose IDC vs FDC and identify at-risk family members
- insensitive method : clinical screening > genetic screening

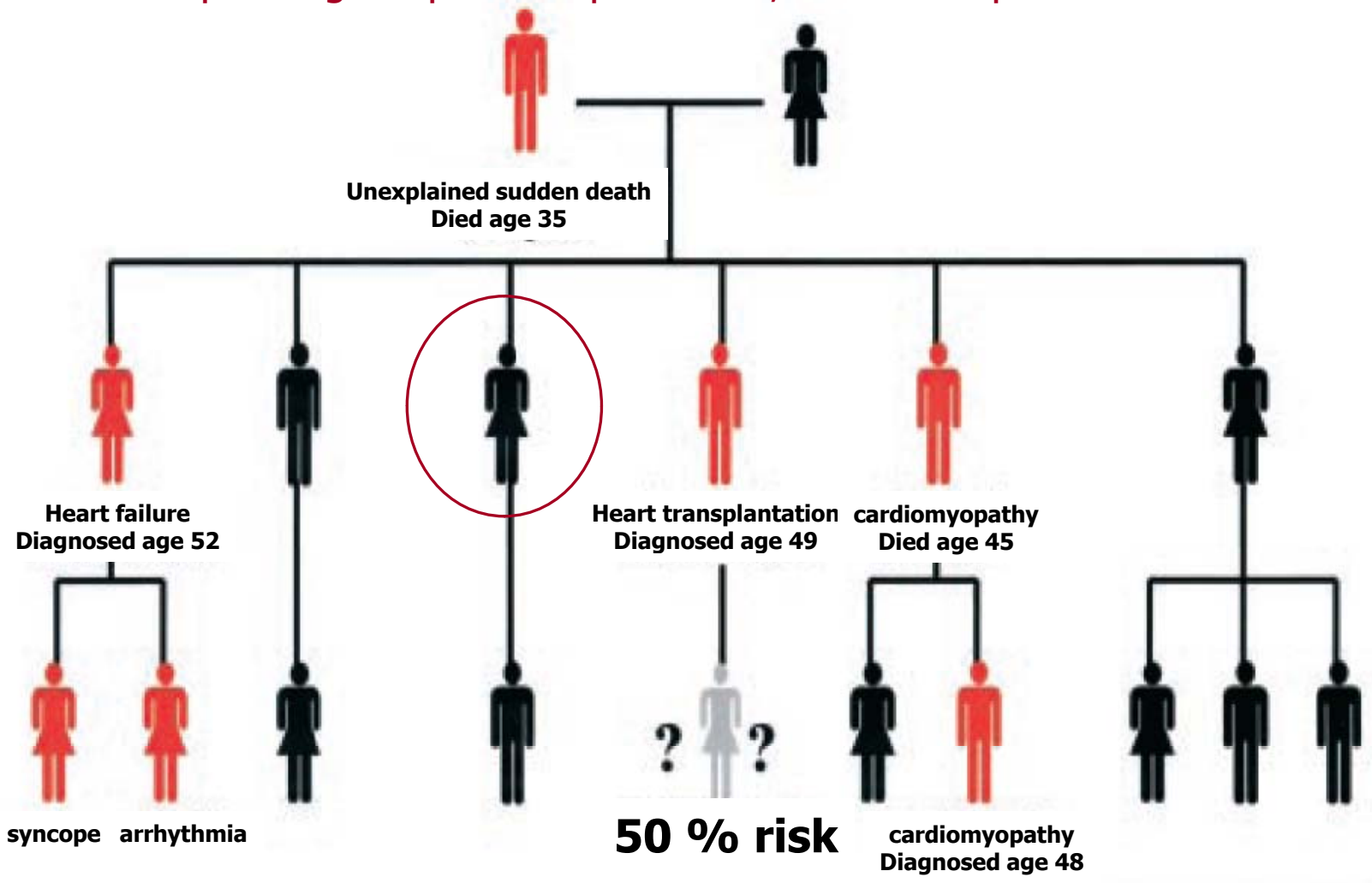
EchoCG and ECG screening

- safe, sensitive, non invasive risk assessment
- early detection of asymptomatic HF or arrhythmia

- all first degree relatives
- ACC/AHA : screening family members should be considered

Dominant Inheritance

FDC: incomplete age-dependent pentrance, variable expression



risk of severe phenotype

Genetic Counseling For FDC

- Definition of genetic counseling

  - communication process

    educational and therapeutic elements

    targeted to pts and their families who face the risk of a genetic dis.

- Genetic counseling session

  - review of FDC : the characteristics, genetics, inheritance pattern

  - family history and pedigree analysis

    : the pattern of inheritance in the family & identify at-risk relatives

  - explanation of the benefits, risks, and limitations

    : clinical and/or genetic test for affected individuals, at-risk relatives

  - psychosocial adjustments

Hansen E et al, J Genet Counseling 2001;10:397-415

Possible Outcomes of Clinical Screening

	If Clinical Screening Normal:	If Clinical Screening Abnormal:
Positive consequences	Relief; removal of some uncertainty No immediate medical costs; insurance is not affected	Relief; removal of some uncertainty
Negative consequences	Survivor guilt possible	Anxiety, guilt, jealousy, anger Anticipation of worsening disease Medical costs; insurability concerns Offspring are at risk
Uncertainties remaining	Possibility of future disease Question of how often to rescreen Offspring remain at risk	Significance of screening results How aggressively to follow up Whether or not to begin treatment

Clinical screening: medical and family history, ECG,EchoCG

Burkett EL et al, J Am Coll Cardiol 2005;45:969-81

Current State of Genetic Test

Currently not widely available for two reasons

- the number of different genes involved in IDC/FDC and the number of different possible mutations in each of these genes makes the development of a comprehensive genetic test difficult
- significant proportion of FDC cases are not attributable to any of the known putative genes, making genetic testing relatively insensitive.

Benefit of Genetic Test

- Confirmation of diagnosis
  - a clinical diagnosis
    negative or inconclusive family history: the only way to confirm FDC.

- Early detection and prevention
  - possibility of prophylactic intervention for mutation carriers

- Exclusion of a causative mutation
  - excluding the mutation in an at-risk family member
    can be extremely beneficial

Limitations of Genetic Testing

- Only limited information about an inherited condition
- Cannot determine
  whether a person will show symptoms of a disorder,
  the severity of the symptoms, or its natural history.
- Prophylactic treatment measures : controversial
  lack of evidences for treatment strategies.
- Limited sensitivity to detect genetic causation

Recommendations for Genetic Testing

1. Genetic testing and mutation screening is not yet available for routine use, partly because of the extensive genetic heterogeneity of the disease.

   However, genetic diagnosis and mutation screening could be performed in families with several affected members through linkage analysis and screening of the candidate genes in the mapped locus.

2. The prevalence of causal genes and mutations has yet to be determined.

   Therefore, given the allelic and locus heterogeneity, routine genetic testing is not feasible in sporadic cases.

3. An ECG and EchoCG should be performed on family members of those with idiopathic DCM for screening.

   Up to 25% of family members may show abnormalities, including isolated LV enlargement with or without systolic dysfunction.

   Pts with LV enlargement and normal systolic function should be monitored routinely with EchoCG

Robin NH et al, Genetic Testing in Cardiovascular Disease. J Am Coll Cardiol 2007;50:727-37

Summary (I)

- 20-50 % of IDC cases: not uncommon
- 16 autosomal & 2 X-linked genes (2005) → over 20 genes (2008)
  : 20-30% genetic causation
- Clinical and genetic data of FDC : Other cardiovascular biology
- Clinical and genetic diagnosis complex
  : incomplete age-dependent penetrance, variable expression, significant locus and allelic heterogeneity
- Family history and pedigree analysis

  - three-generation pedigree : obvious history of DCM or HF
  - diagnose IDC vs FDC, and identify at-risk family members

  - insensitive method : clinical screening > genetic screening

Important Clues in Family History

- History of DCM
- History of heart failure and its symptoms
  shortness of breath, fluid retention of ankles and legs, fatigue/tiredness
- Unexplained sudden death/ cardiac arrest
  some people will mistakenly call sudden death a heart attack, which is caused by CAD, when it might really be caused by DCM
- Muscle problems
  cramps, stiffness, history of muscular dystrophy
- Heart rhythm or conduction problems
  including those that require implantation of a defibrillator or pacemaker
- Palpitations
- Syncope
- Young age of onset in any of the above

Summary (II)

- EchoCG & ECG screening of first-degree relatives with IDC & FDC

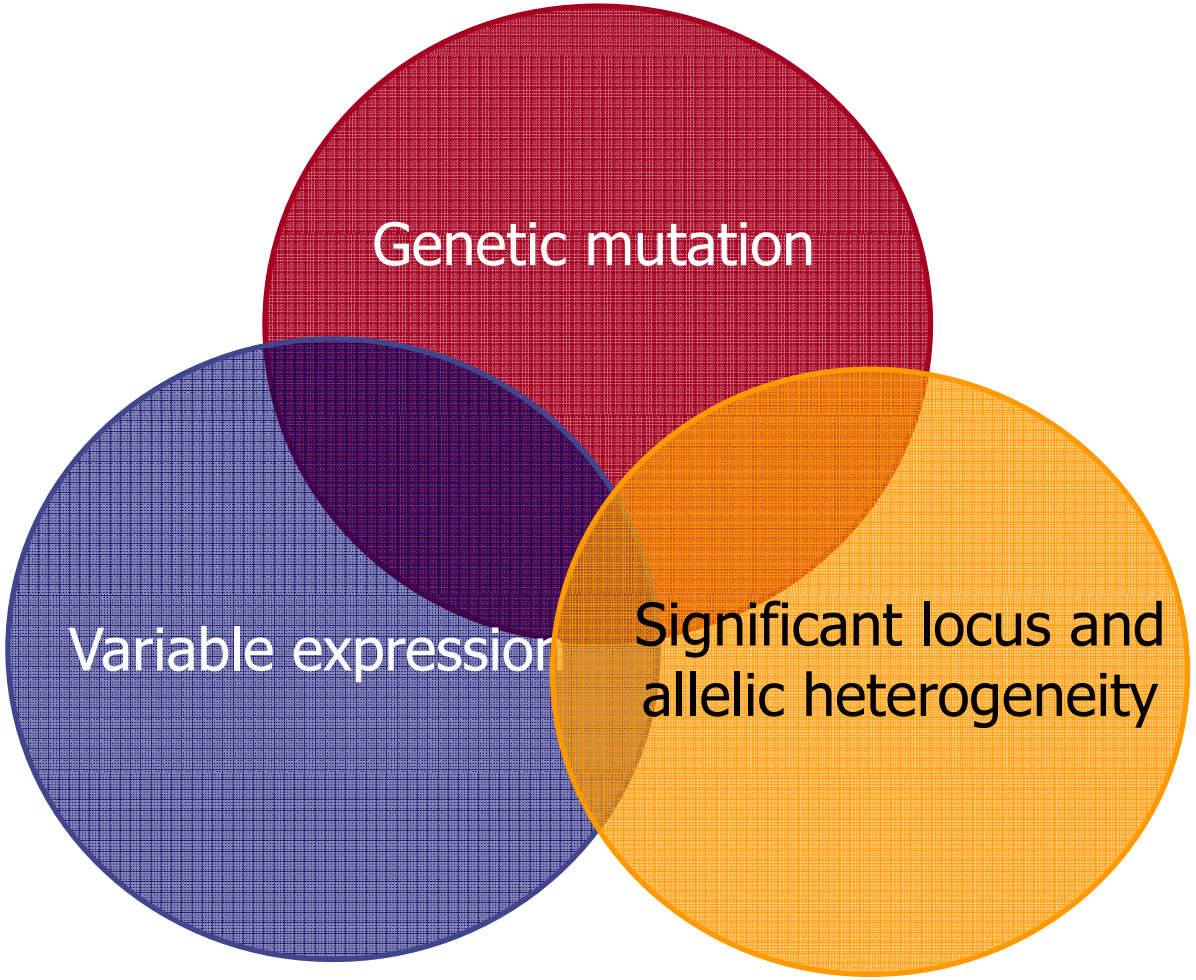
  : early detection, possible Tx before advanced symptomatic dis.

- Genetic counseling for IDC & FDC is also indicated

  : to assist with family evaluation for genetic disease
  with the uncertainty & anxiety

- Genetic testing : new opportunities for presymptomatic diagnosis

FDC : clinical and genetic diagnosis complex



Perspectives: Injury-Response of FDC

- Genetic : genetic predisposition
- Pressure/volume overload
- and viral, toxin, ischemia (environment)
- Danger signal → Host response
  Innate immunity
- Remodeling process: adaptation
  compensation

New Insight into D-CMP. ACC Apr. 1 2008