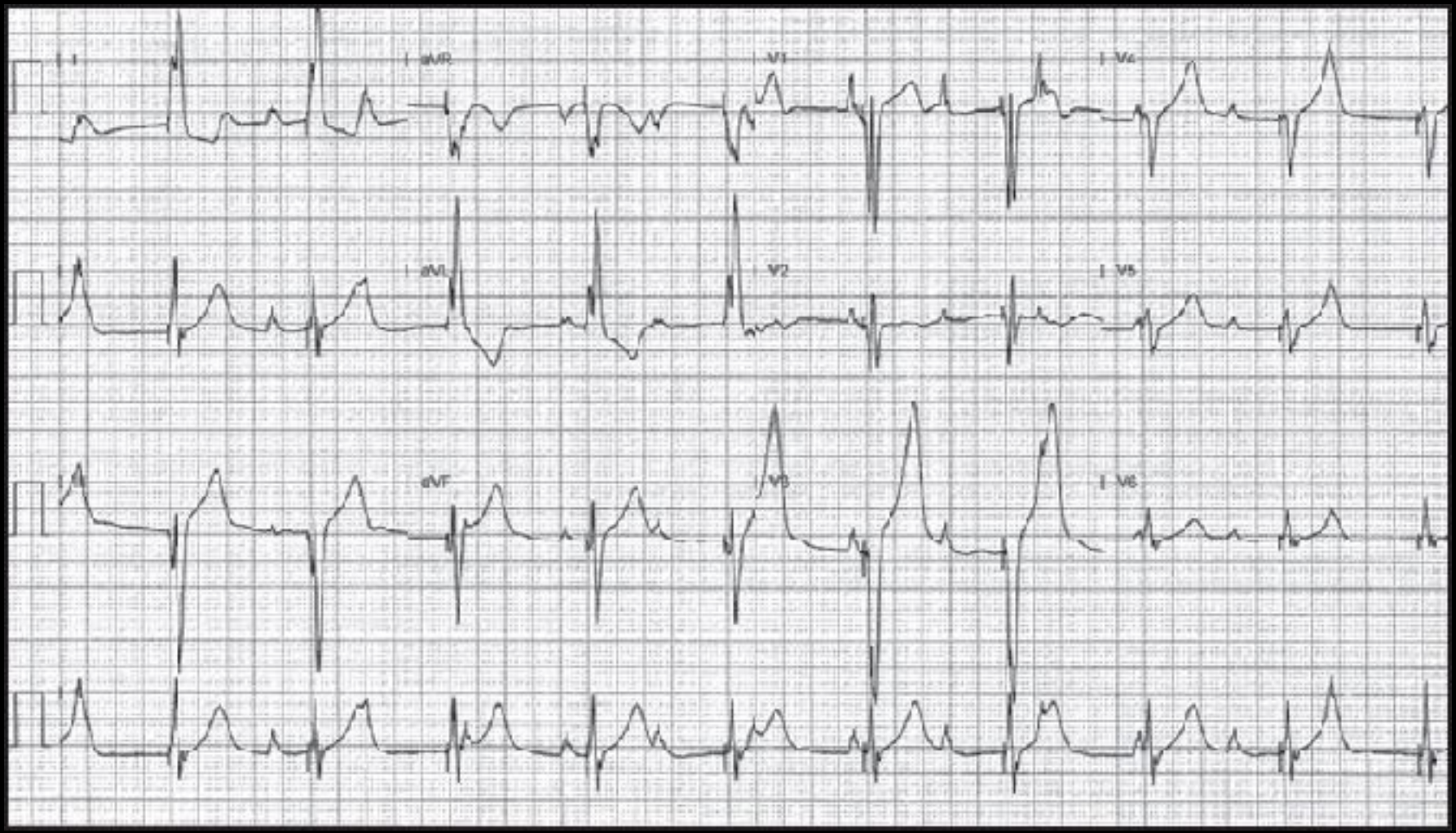
PRKAG2 Syndrome

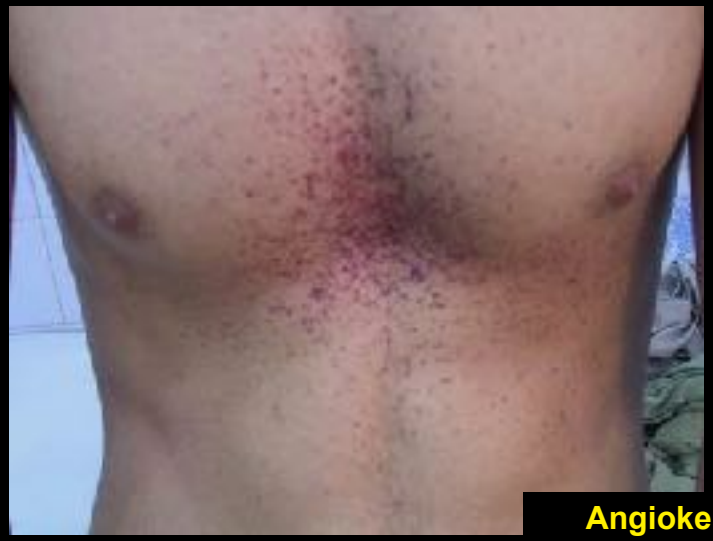
Post ablation day 6 with heart block and VA S/P AICD

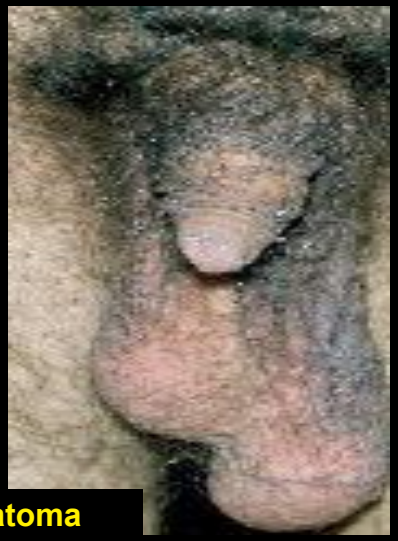


Fabry's

- X-linked recessive with incomplete penetrance metabolic disorder
- Mutation of *GLA* causing deficiency of alpha-galactosidase A
- Accumulation of globotriaosylceramide in skin, kidney, nervous system, cornea and heart
- Cardiac findings :
  - Aortic root dilation, asymmetric increased wall thickness, LV systolic dysfunction
  - Binary appearance
  - Double peak on strain

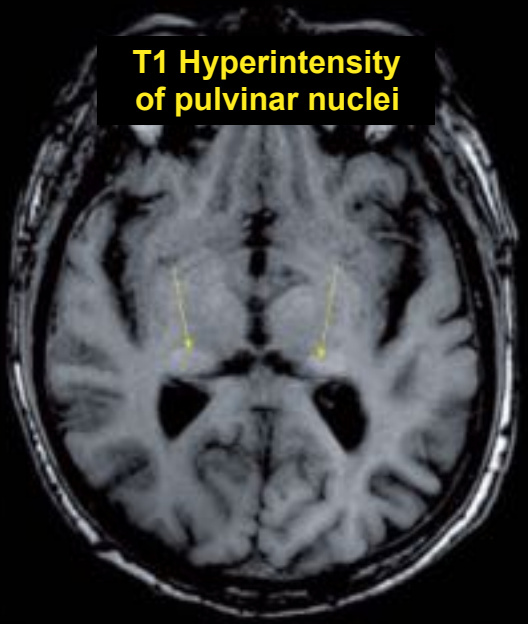
Fabry Disease





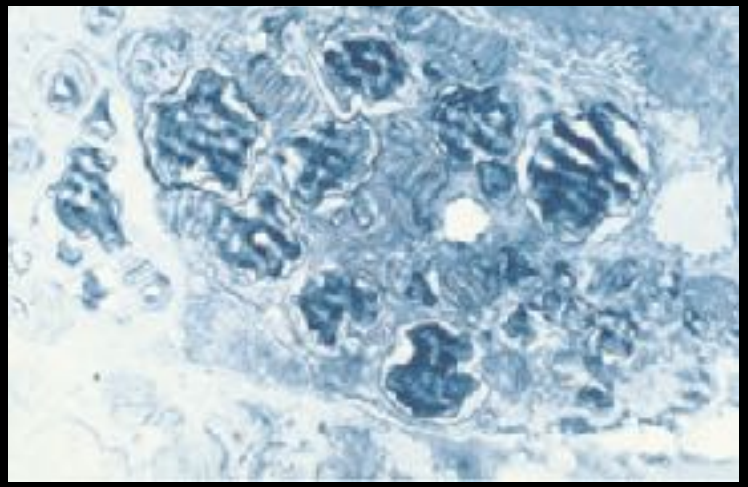
Angiokeratoma

Cornea verticilata

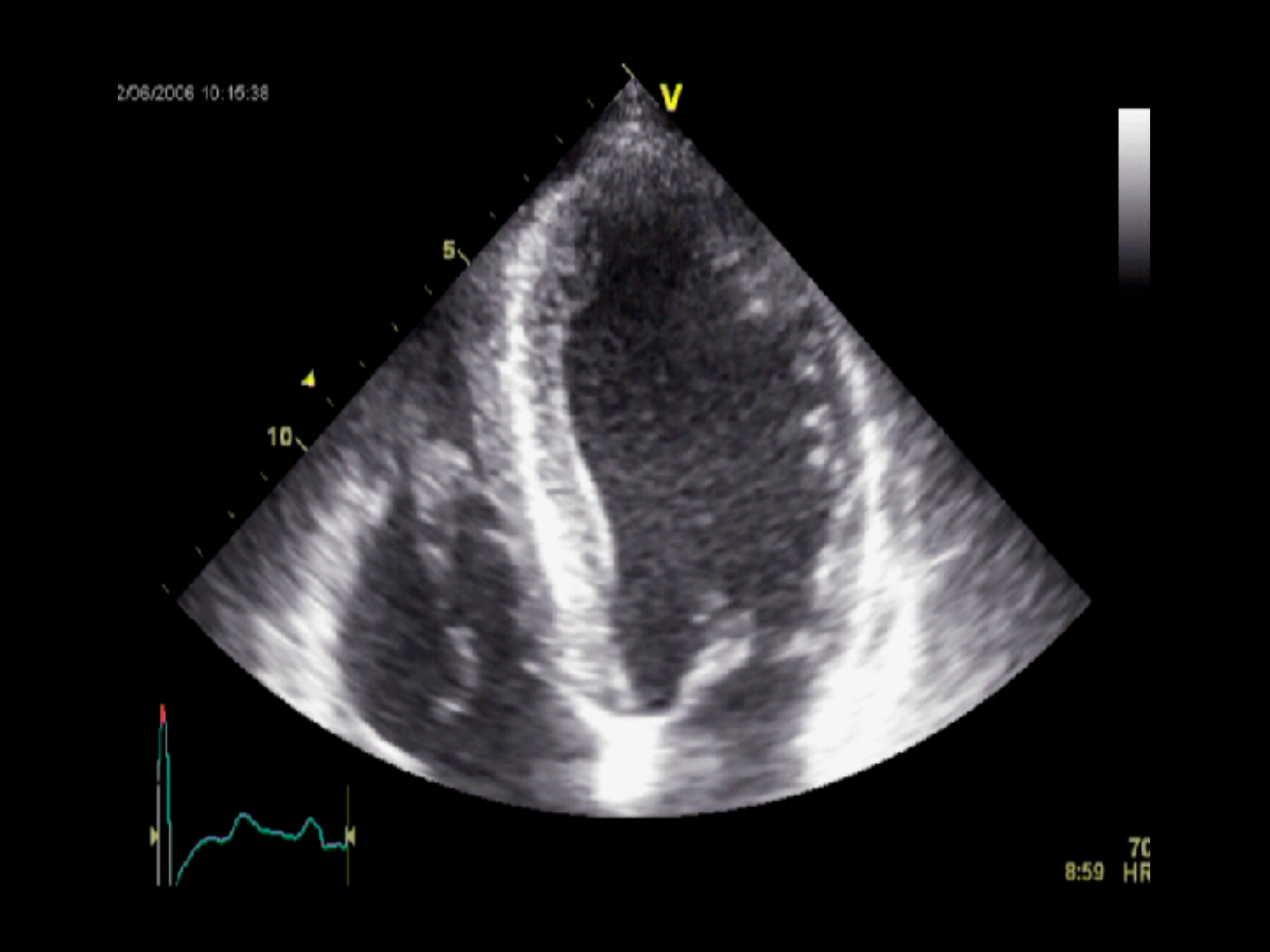


T1 Hyperintensity
of pulvinar nuclei

Proteinuria / Renal failure
GL3 (globotriaosylceramide) deposition



Hypohidrosis
Acroparesthesia
Hearing loss
Tinnitus
Early stork/TIA
GI dysmotility


2/06/2006 10:16:38
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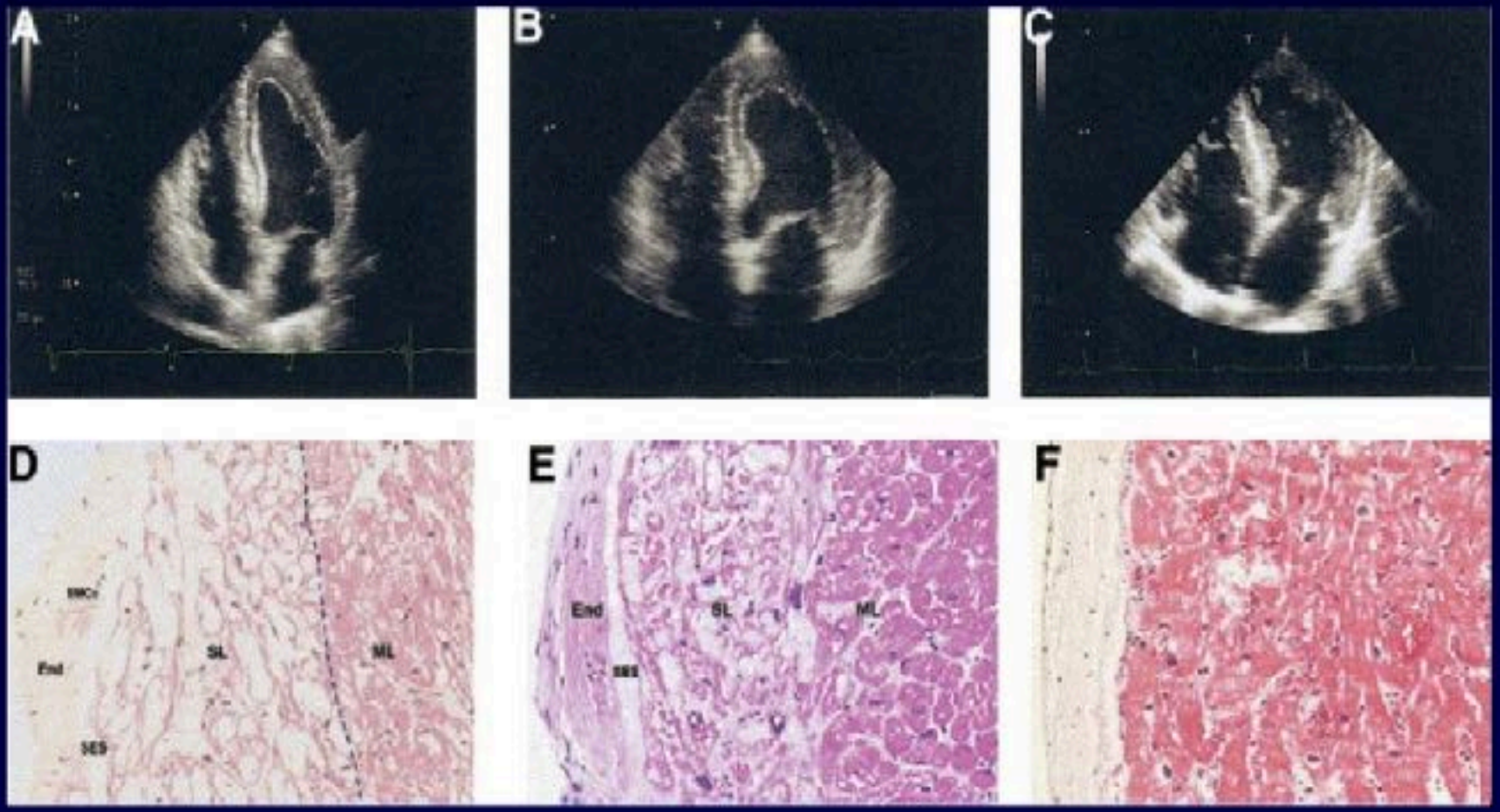
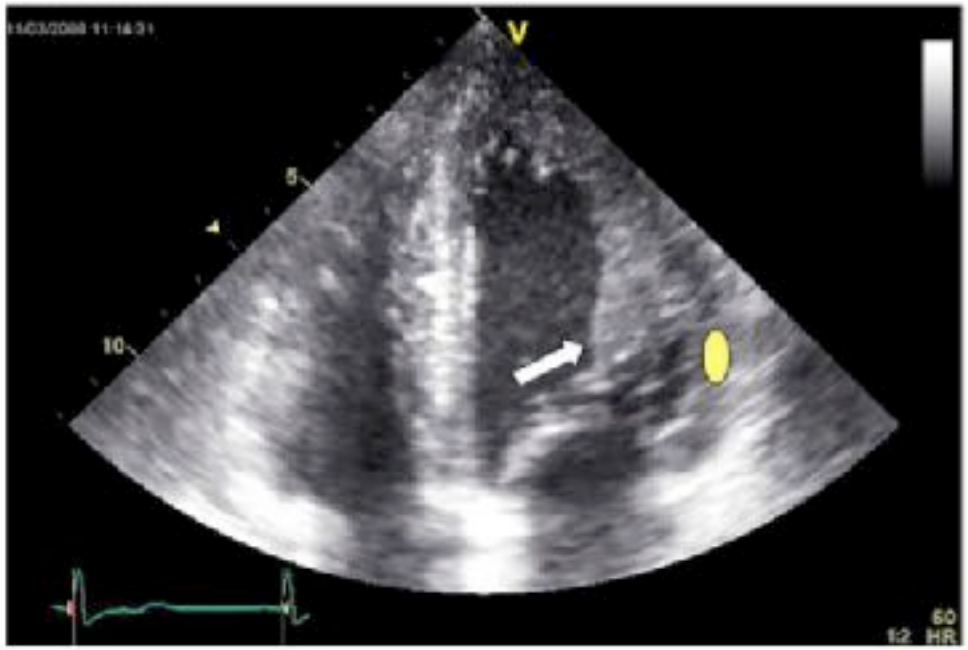
JACC Journals

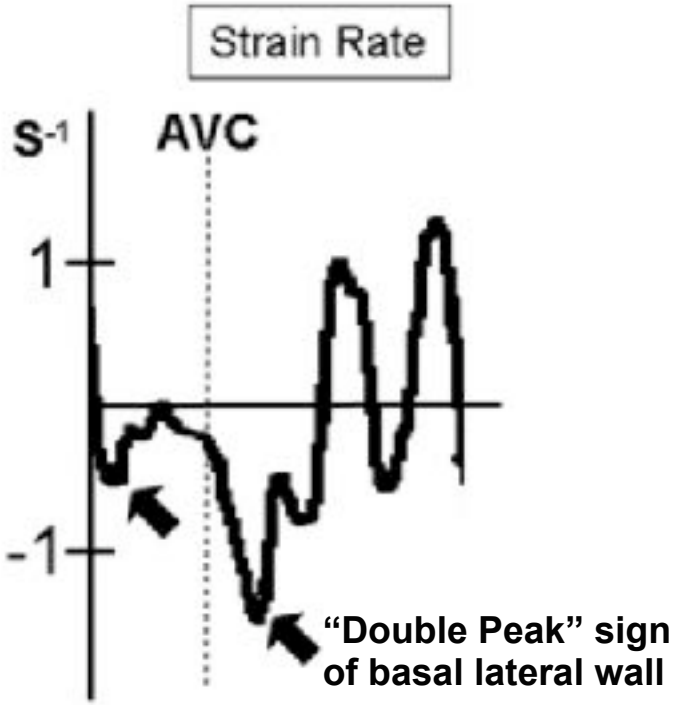
From: Fabry's Disease Cardiomyopathy: Echocardiographic Detection of Endomyocardial Glycosphingolipid Compartmentalization

J Am Coll Cardiol. 2006;47(8):1663-1671. doi:10.1016/j.jacc.2005.11.070

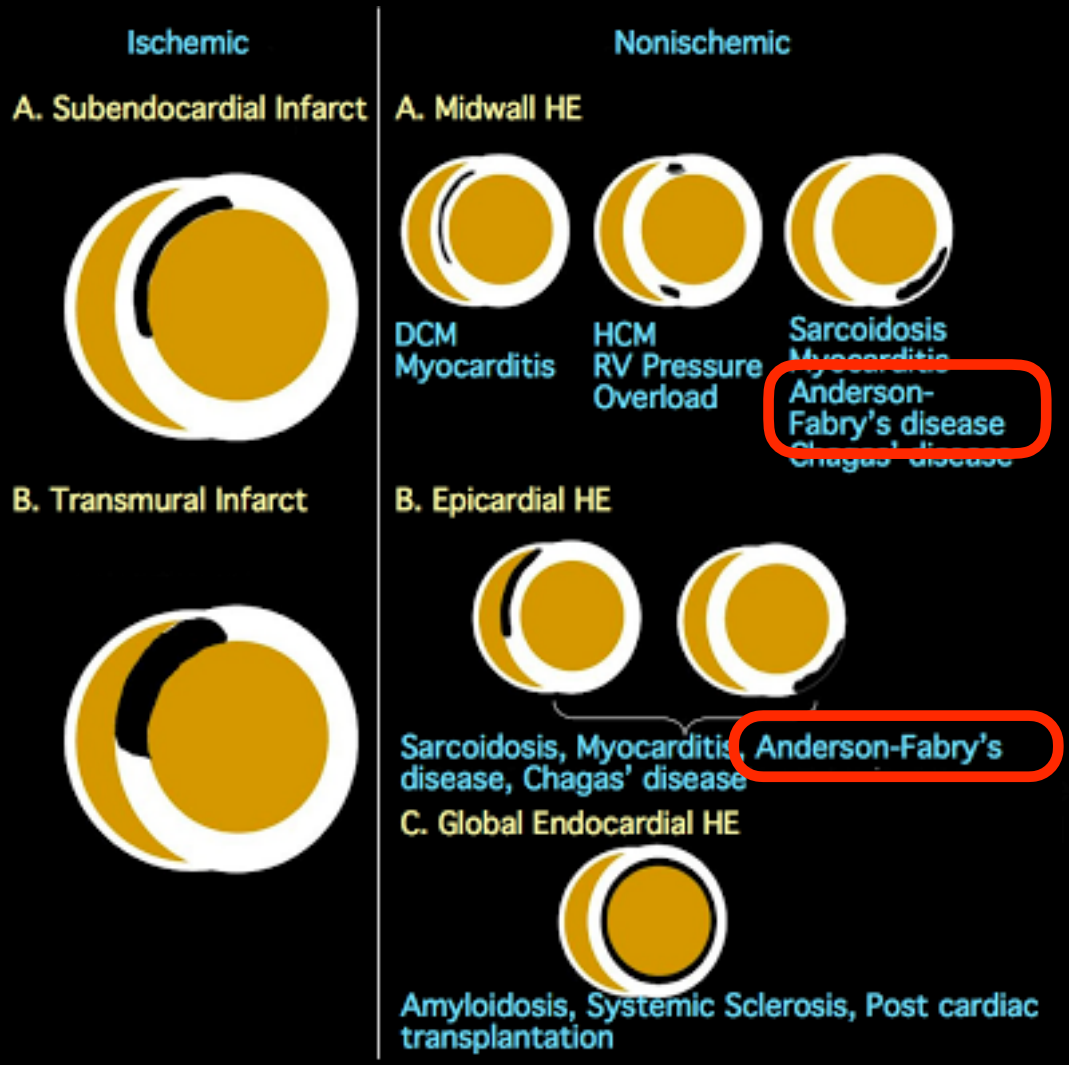


Strain Rate of Fabry's dz

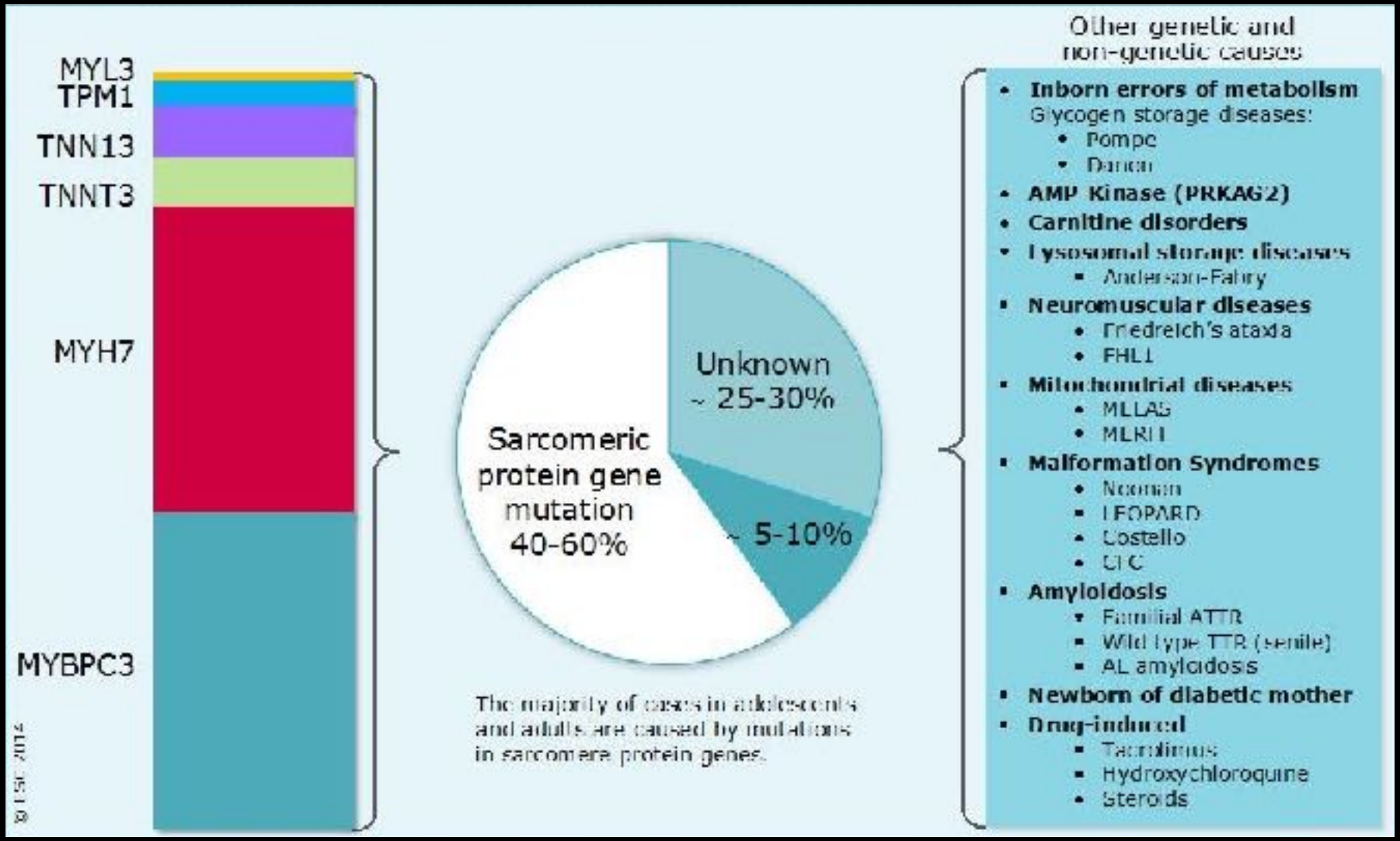




CMR with LGE in Fabry

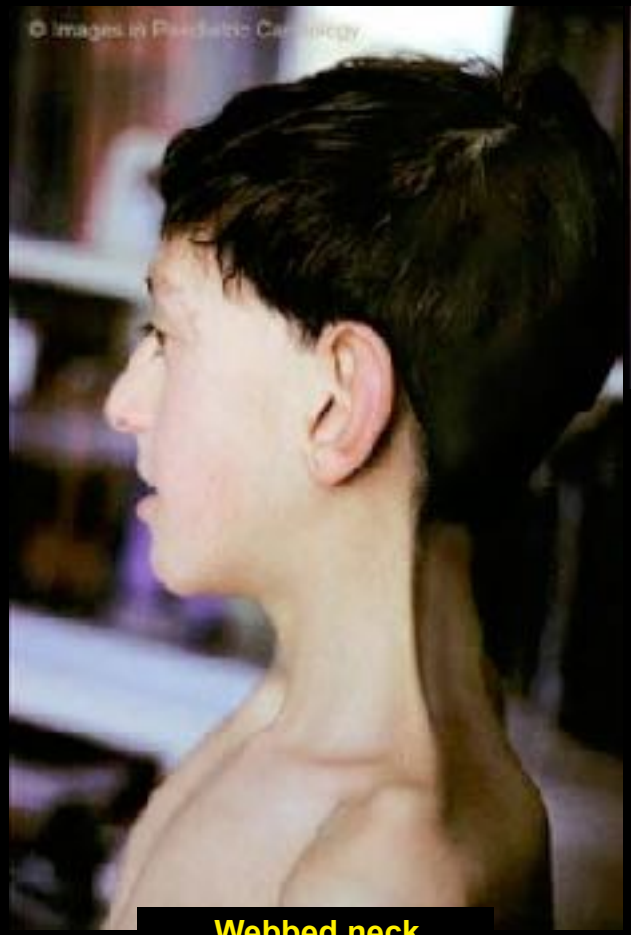


Etiology of Hypertrophic Cardiomyopathy



Syndromic HCM

Noonan syndrome

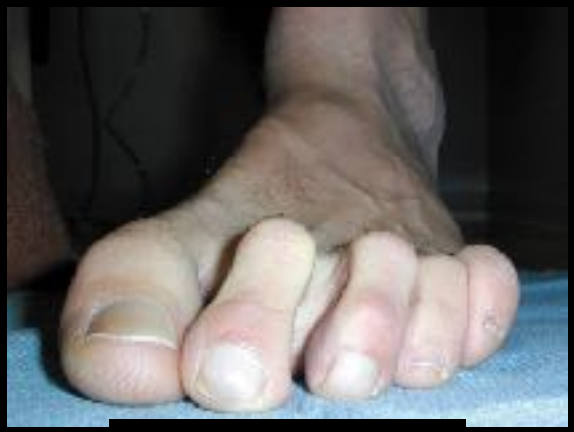


Webbed neck

LEOPARD

Lentigines

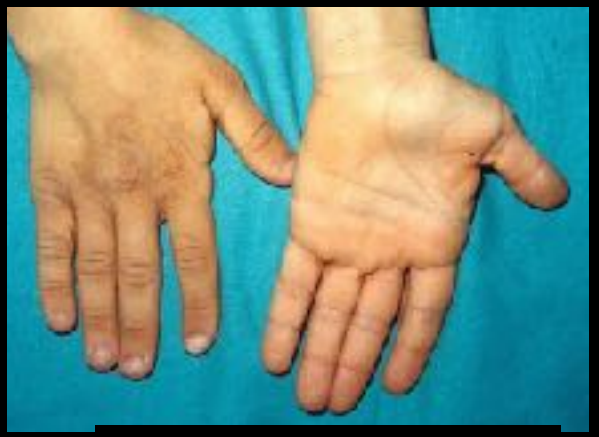
Friedreich's ataxia



Hammer toes

Costello syndrome

Large mouth, thick lips

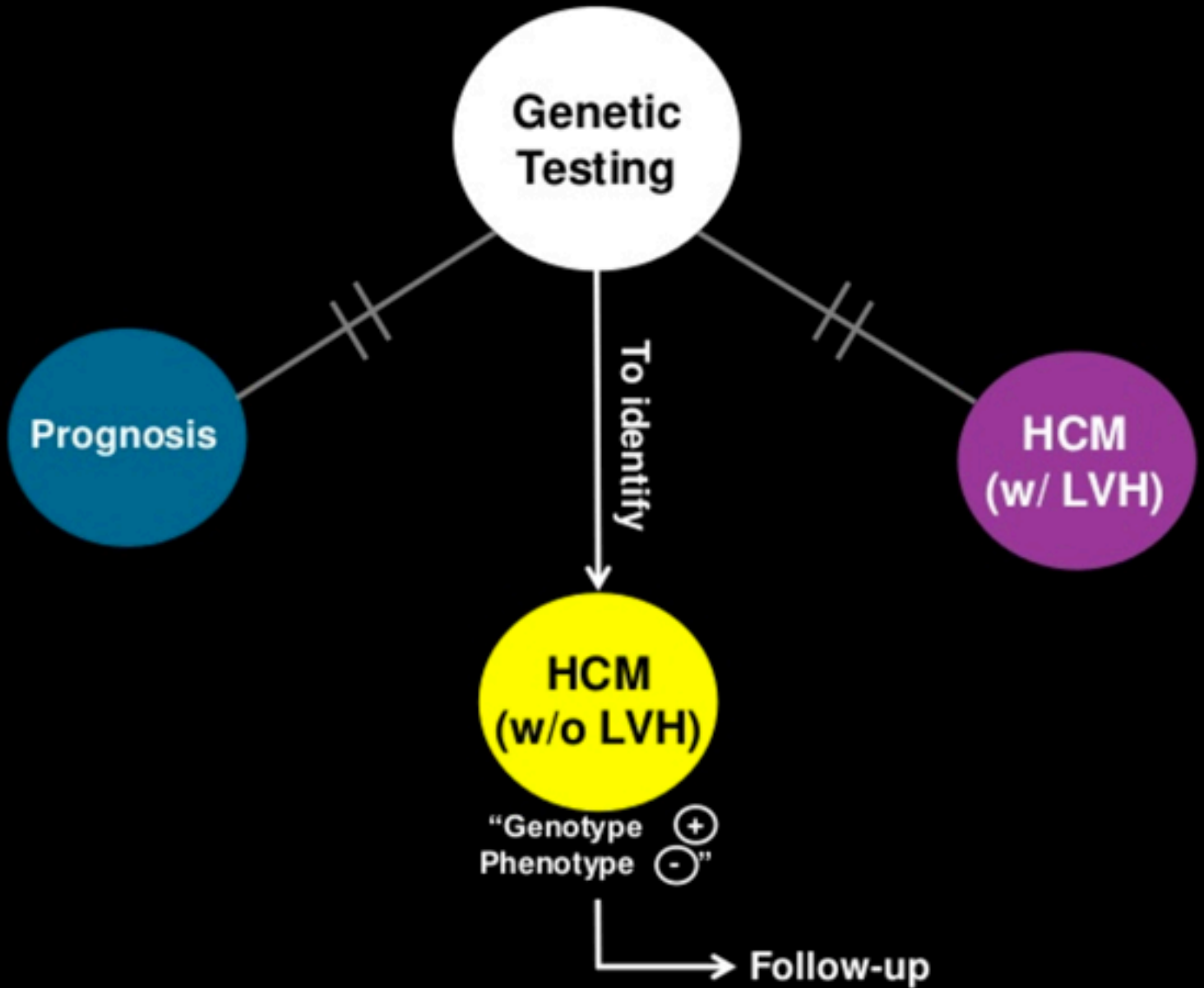


Excessive skin dorsum
Deep palmar crease

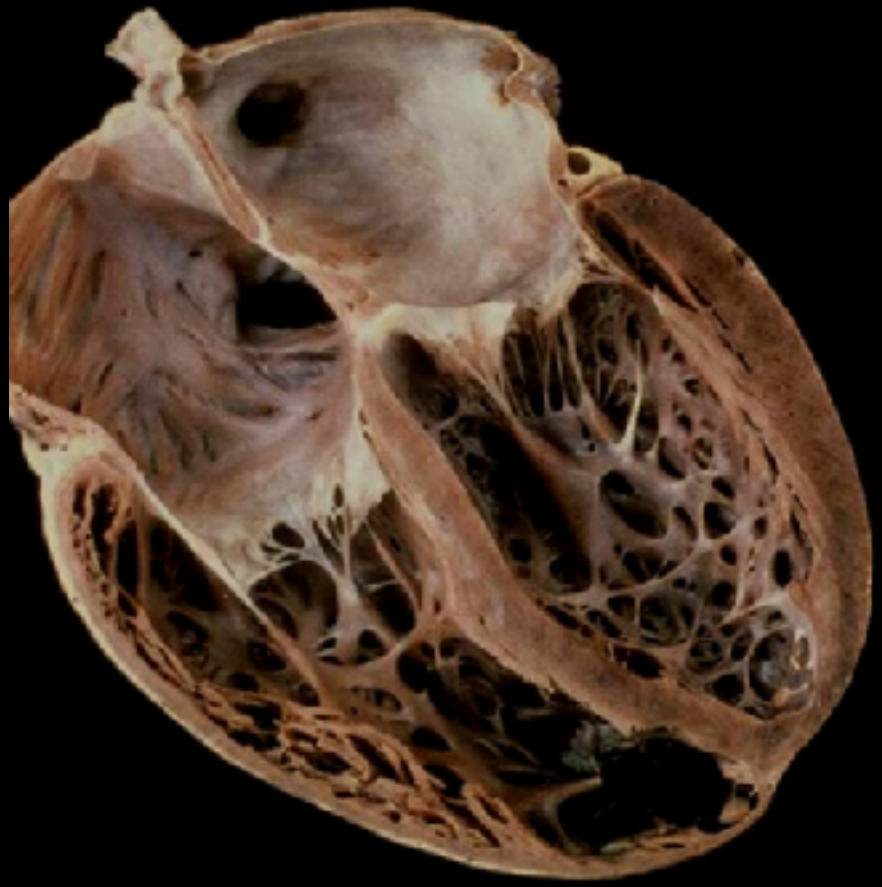
Therapeutic options

Anderson-Fabry disease	Recombinant human α-galactosidase A
Friedreich ataxia	Idebenone
Transthyretin amyloidosis	Tafamidis, Diflunisal and Doxycycline/TUDCA
Pompe disease	Alglucosidase alpha
Type 1 tyrosinemia	Nutritional restriction
Tacrolimus-induced HCM	dose reduction/discontinuation
Danon disease	Heart transplantation

Nat Review Cardiology 2016


Genetic Testing
Prognosis
To identify
HCM (w/ LVH)
HCM (w/o LVH)
"Genotype +
Phenotype -"
Follow-up

Dilated Cardiomyopathy



Familial DCM

Cytoskeletal genes
- Dystrophin
- Desmin
- Metavinculin
- Sarcoglycan complex
- CRYAB
- Epicardin

Z-Band
- LIM protein
- TCAP

Muscular dystrophy
- Becker (dystrophin)
- Duchene (dystrophin)
- Emery-Dreifuss

SCN5A Mutation

Hemochromatosis

Nuclear membrane
- Lamin A/C (LMNA)
- Emerin

Mitochondrial cytopathies

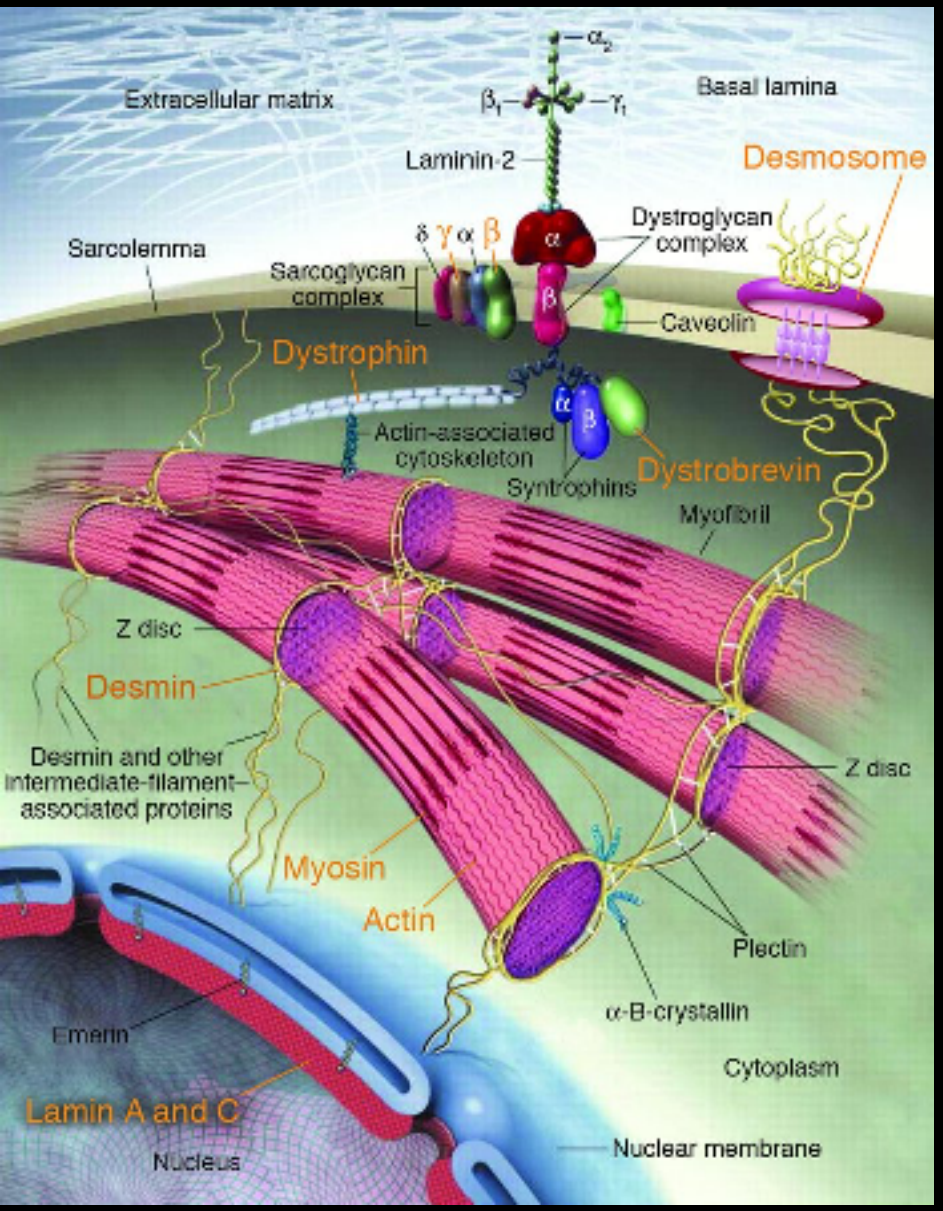
Intercalated disc protein mutation

Sarcoplasmic protein mutations

Familial, Unknown gene

Mahidol University

European Heart Journal 2008;29:270-276



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Truncations of Titin Causing Dilated Cardiomyopathy

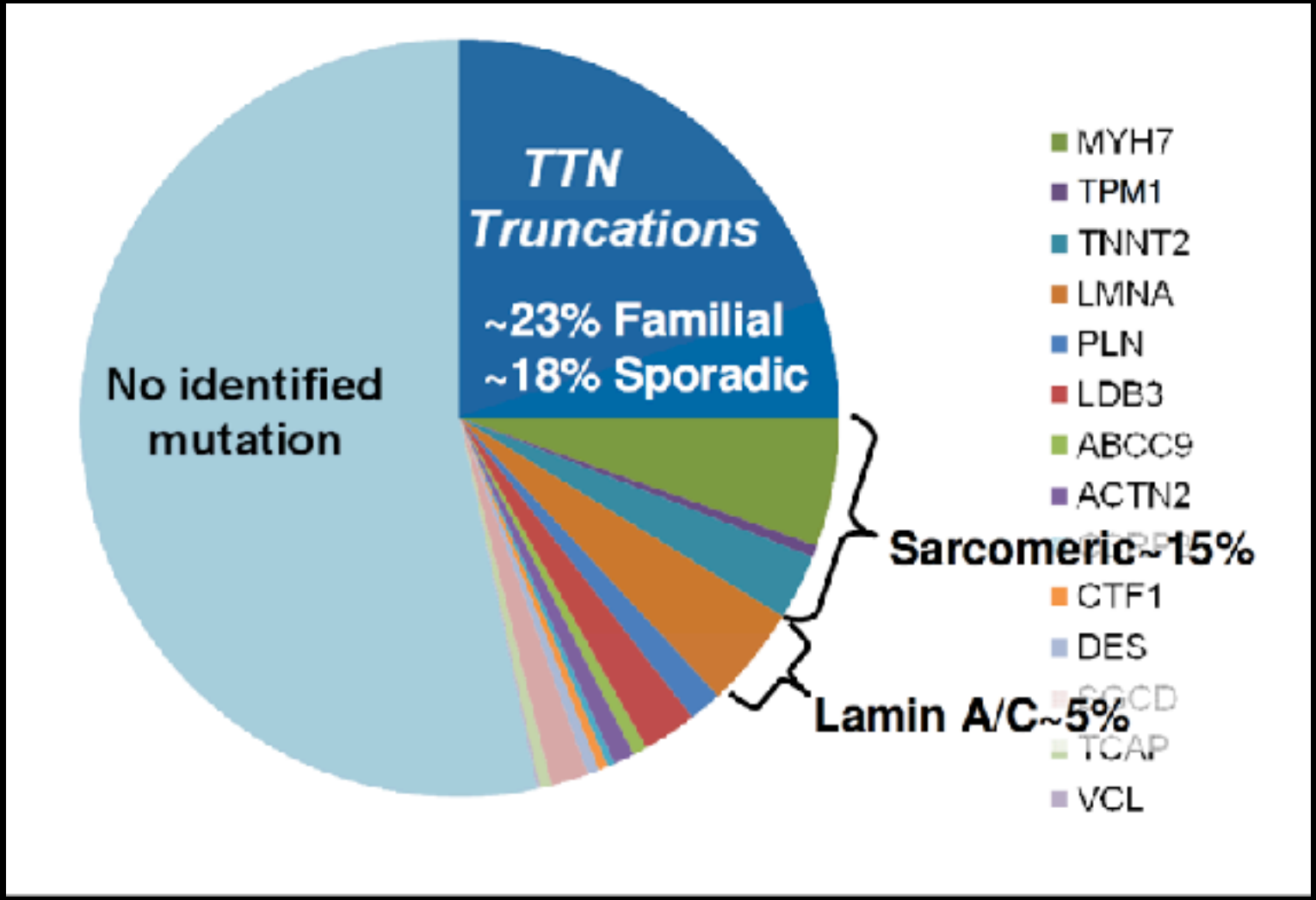
CONCLUSIONS

TTN truncating mutations are a common cause of dilated cardiomyopathy, occurring in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 13% of sporadic cases. Incorporation of sequencing approaches that detect *TTN* trun-

Morita JCI. 2005;115: 518

N Engl J Med 2012;366:619-28.

Genetic Contributors to DCM



Zimmerman Genet Med. 2010

Herman NEJM 2012

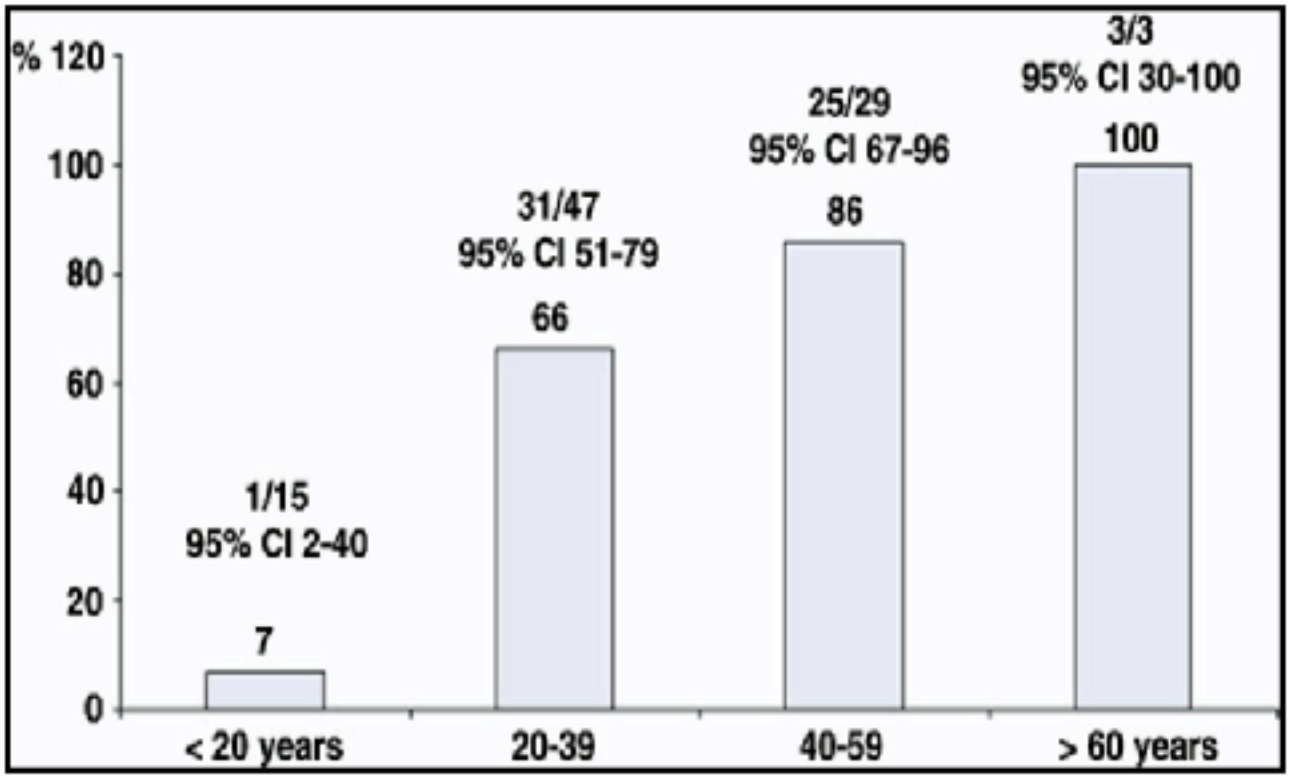
Associated Clinical Features Present in a Minority of Patients with DCM

Associated Phenotype	Clinical Features	Comment	Associated Gene*
Conduction disease	Sinus arrest AV block Interventricular block	May precede DCM	*DES* *DMD* *EMD* *LMNA* *SCN5A*
Supraventricular arrhythmia prior to DCM	Premature atrial contraction Atrial fibrillation	Often with slow ventricular response	*EMD* *LMNA* *SCN5A*
Skeletal Myopathy	Limb Girdle Emery- Dreifuss Myotonic Dystrophy Duchenne/ Becker Myofibrillar Myopathy	Proximal muscle weakness Contractures, skeletal myopathy and wasting Myotonia, weakness, baldness and cataracts. Progressive X-linked proximal myopathy Slowly progressive proximal and distal weakness	*LMNA* *EMD, LMNA* *ZNF9, DMPK1* *DMD* *DES*
Hearing loss	Sensorineural hearing loss	Hearing loss typically occurs in 1st and 2nd decade of life	*EYA*
Palmoplantar keratoderma	Increased thickness of the palms and soles with woolly or excessively curly hair	May precede cardiac involvement	*DSP*

Lakdawala NK Circ Arrhythm Electrophysiol 2012

Cardiolaminopathy - DCM caused by LMNA Mutations

Age associated Penetrance



Clinical Manifestations	Sinus Bradycardia PAC	▶ AVB AF	▶ DCM VT, SCD

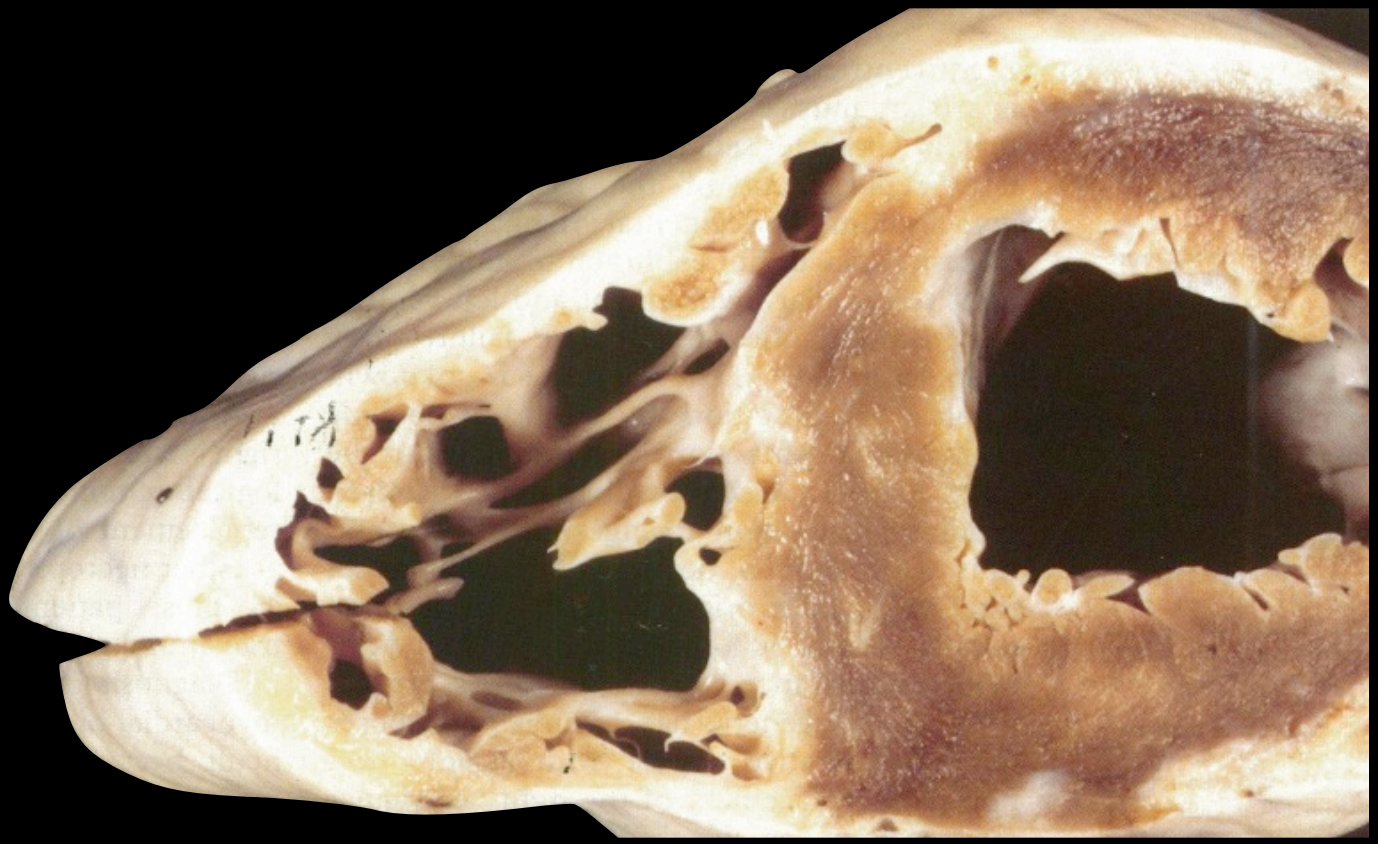
Pasotti M JACC 2008;52:1250

Barth syndrome

- X-linked inborn error metabolism
- Mutations in *TAZ* gene that codes for tafazzin
- Tafazzin = phospholipid transacylase located in the inner mitochondrial membrane —> cardiolipin remodeling
- Clinical :
  - Cardiomyopathy : DCM or LVNC
  - Skeletal myopathy
  - Growth retardation
  - Neutropenia
  - Increased urinary levels of 3-methylglutaconic acid

Semin Med Genet (2013) 163C:198–205

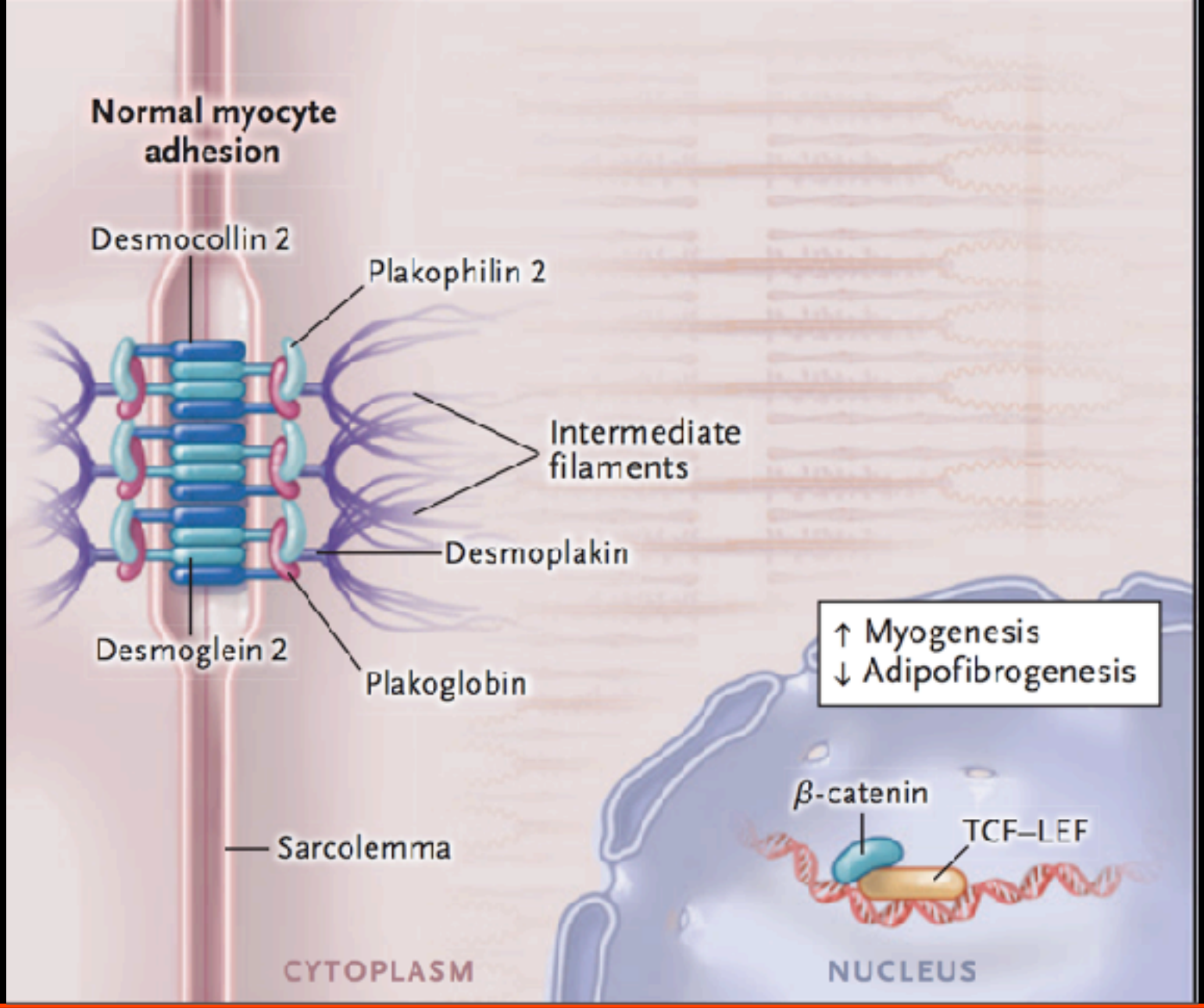
Arrythmogenic Right Ventricular Cardiomyopathy



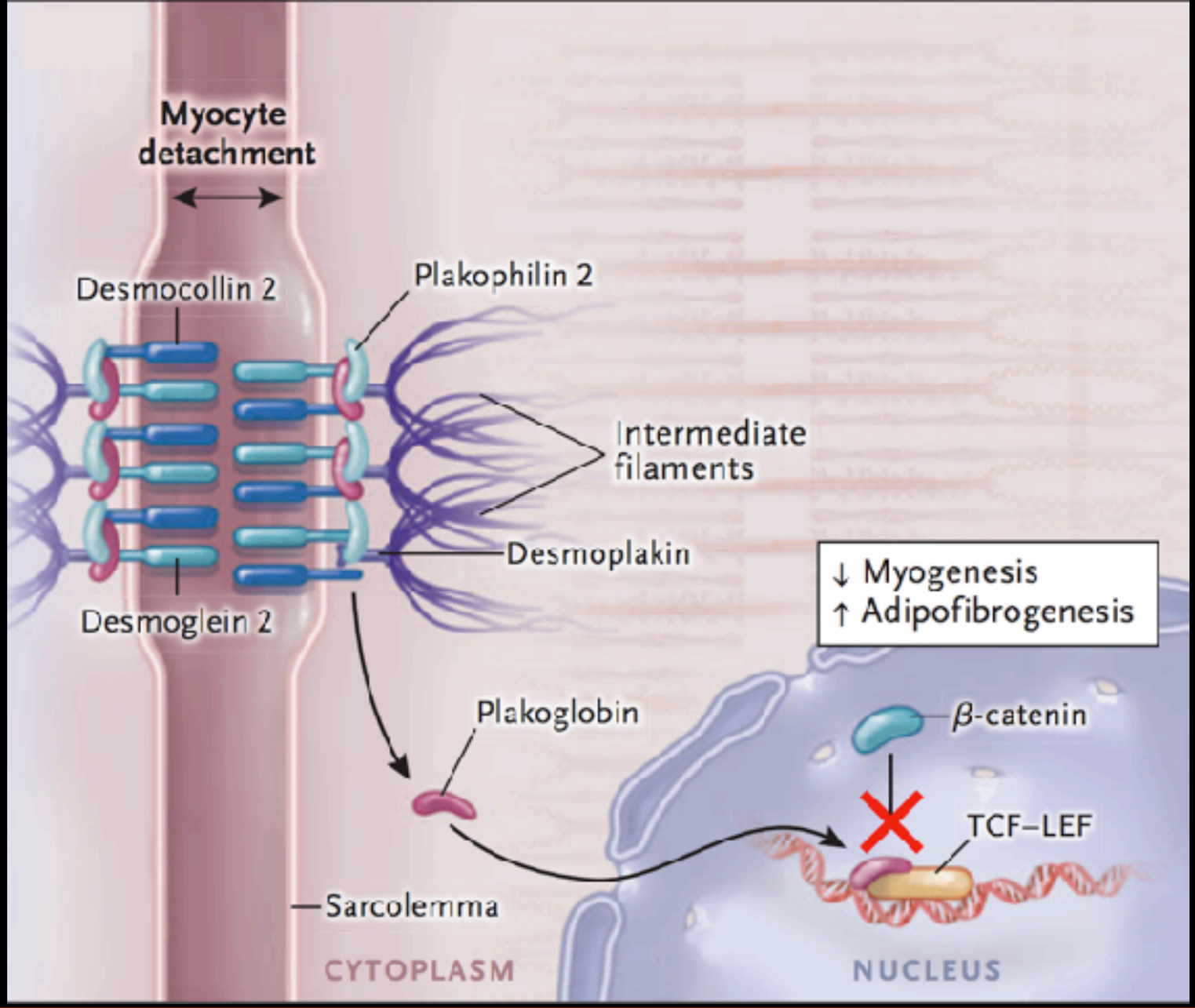
Arrythmogenic Right Ventricular Cardiomyopathy

- Genetic/Familial cardiomyopathy caused by desmosomal dysfunction and characterized by progressive loss of RV myocardium and fibrofatty replacement
- Associated with ventricular tachyarrythmias of RV origins
- A leading cause of sudden death
- Prevalence ~ 1:5000

N Engl J Med. 2017 Jan 5;376(1):61-72

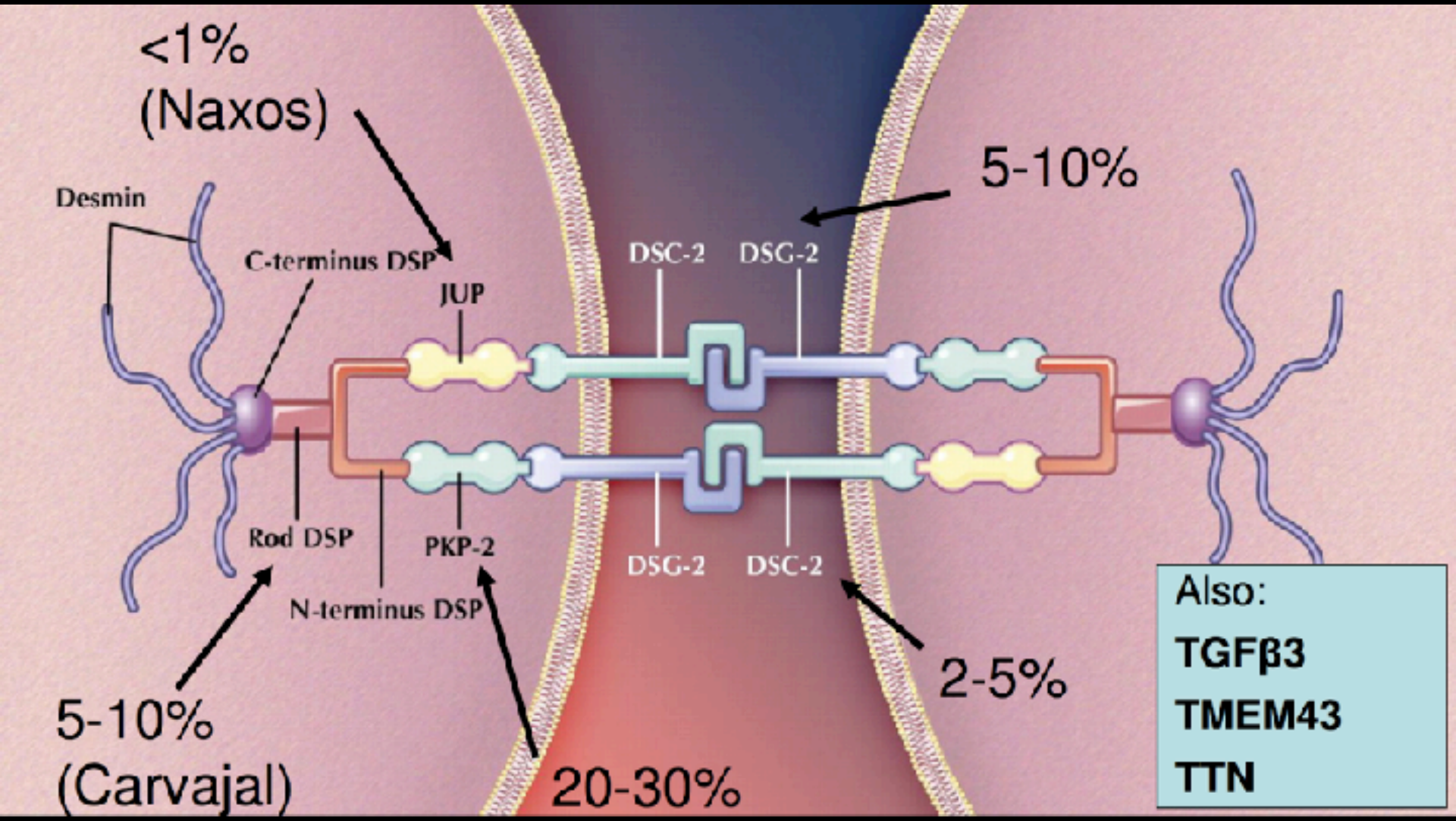


N Engl J Med. 2017 Jan 5;376(1):61-72



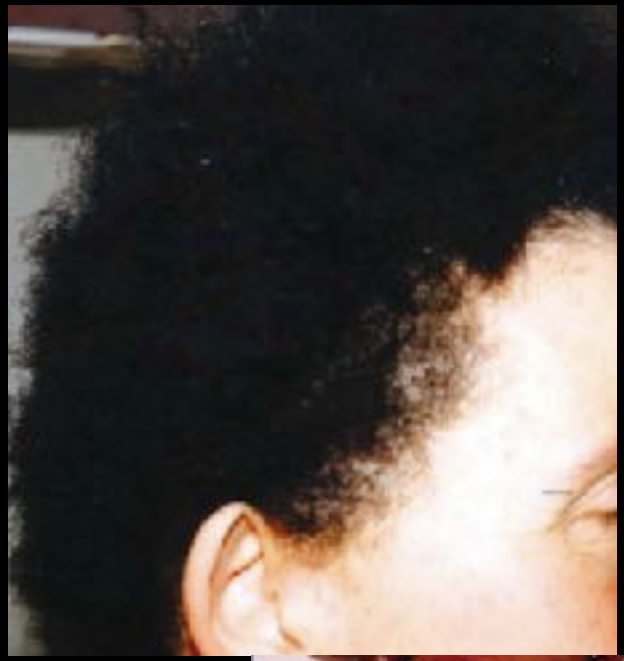
N Engl J Med. 2017 Jan 5;376(1):61-72

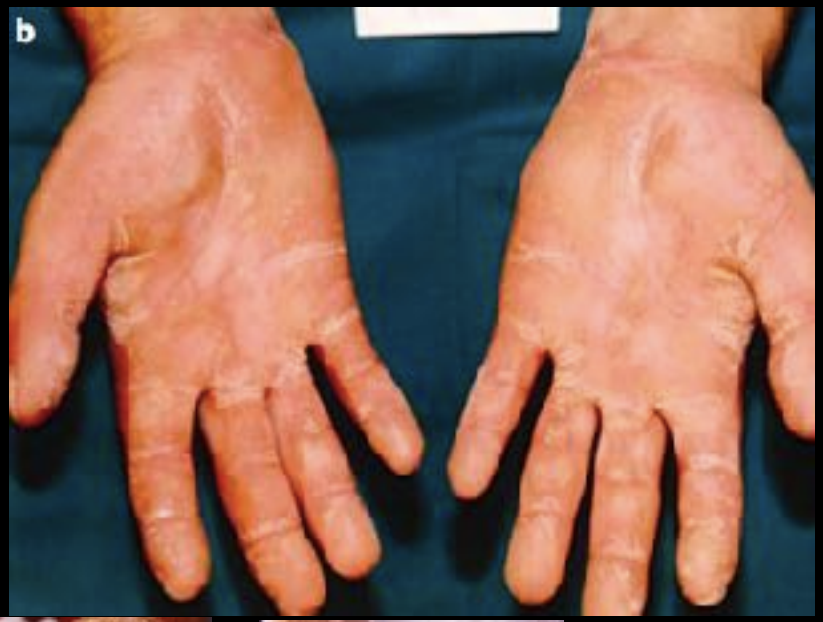
Arrythmogenic Right Ventricular Cardiomyopathy

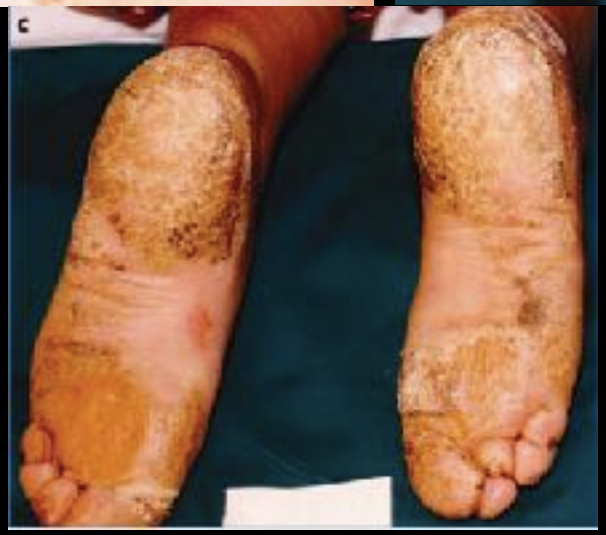


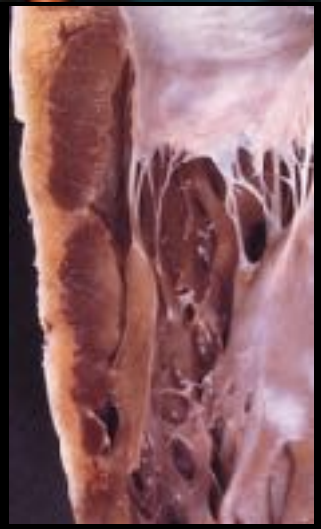
N Engl J Med. 2017 Jan 5;376(1):61-72

Naxos disease





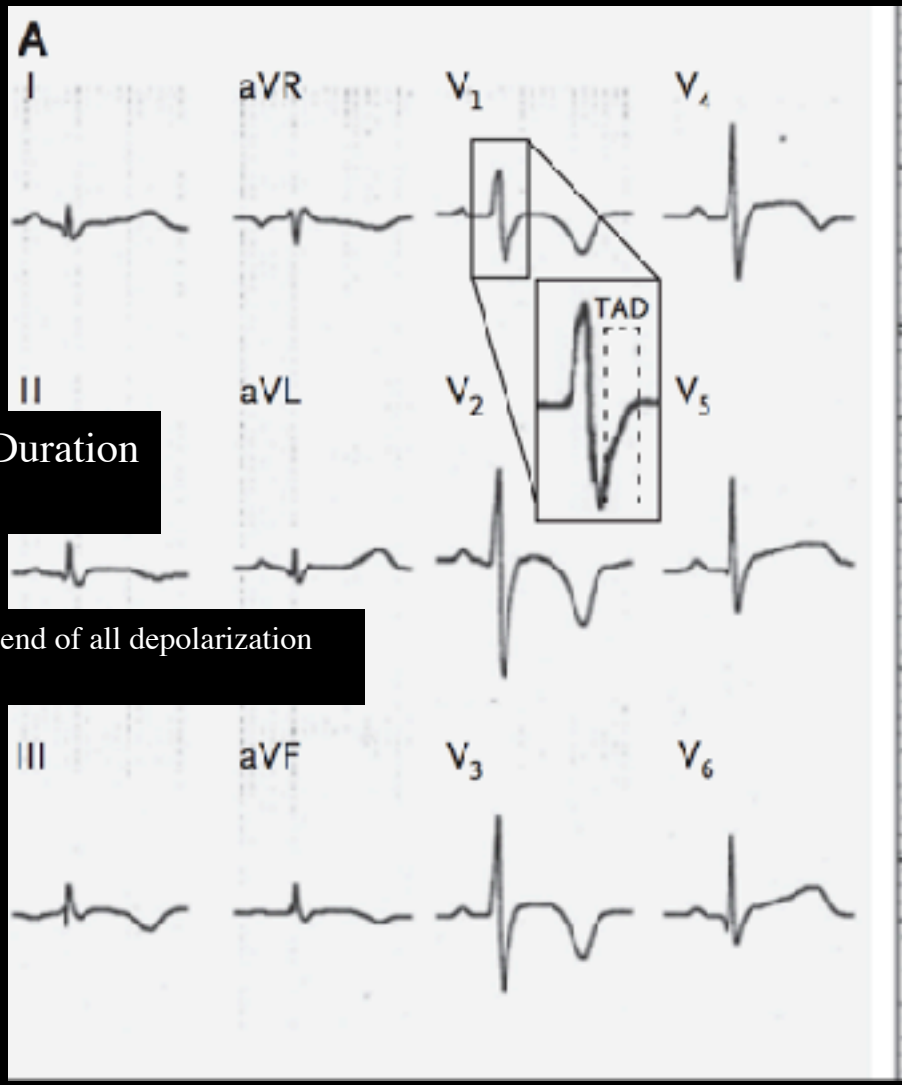


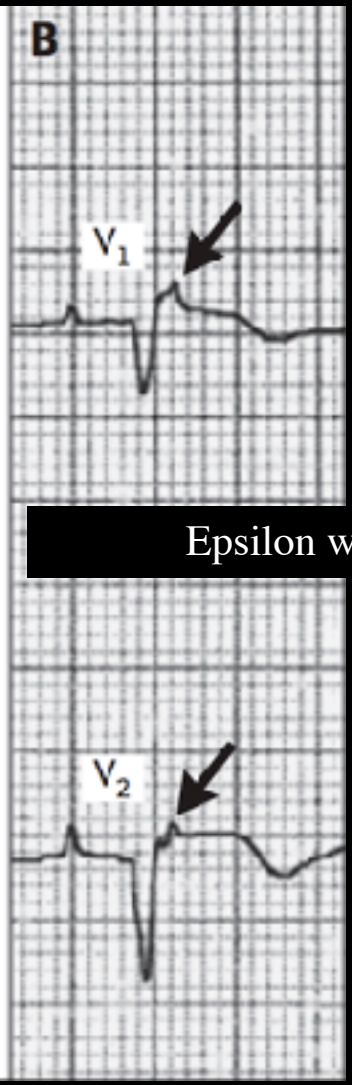


ECG Findings of ARVC

Terminal Activation Duration (TAD)

Nadir of the S wave and the end of all depolarization deflections > 55 msec

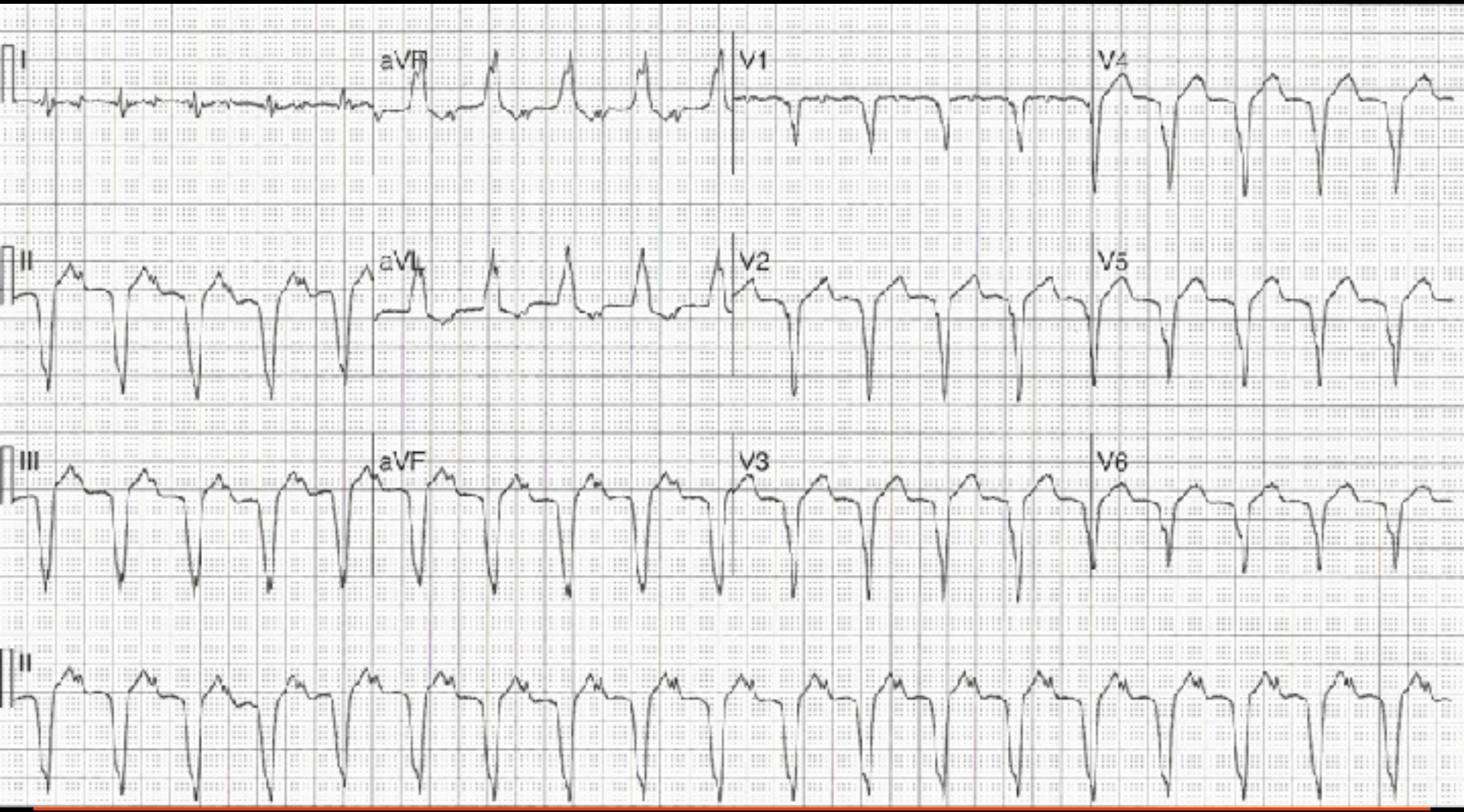




Epsilon wave

N Engl J Med. 2017 Jan 5;376(1):61-72

Typical VT in ARVC
LBBB/superior axis



N Engl J Med. 2017 Jan 5;376(1):61-72

Imaging Criteria for ARVC

By 2D echo:

- Regional RV akinesia, dyskinesia, or aneurysm
- *and* 1 of the following (end diastole):
  - PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2)
  - PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2)
  - *or* fractional area change ≤33%

N Engl J Med. 2017 Jan 5;376(1):61-72

Imaging Criteria for ARVC

By MRI:

- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction
- *and* 1 of the following:
  - Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
  - *or* RV ejection fraction ≤40%

By RV angiography:

- Regional RV akinesia, dyskinesia, or aneurysm

Eur H J 2010;31:806-814

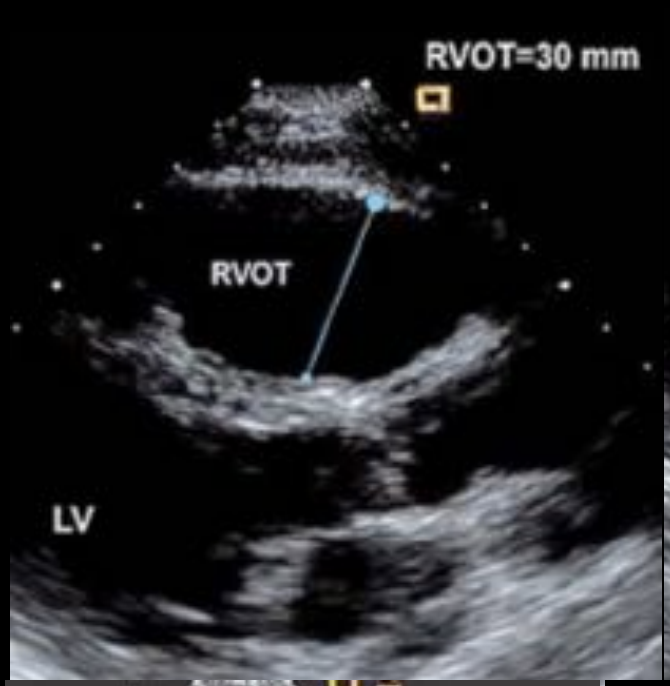
Classic echo

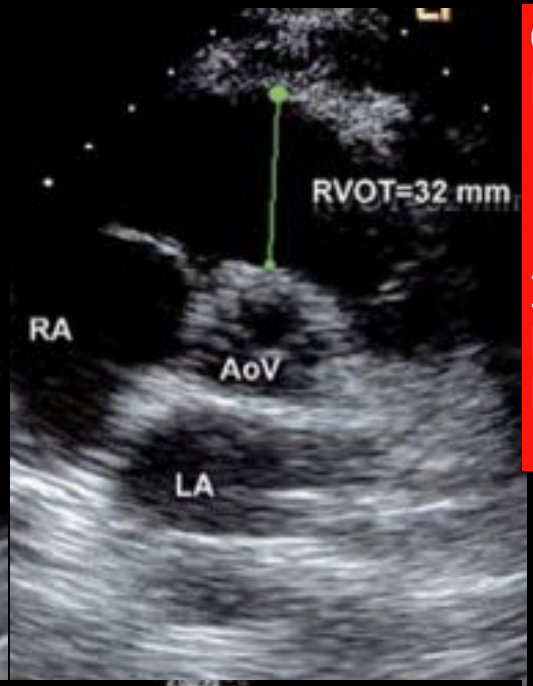
Enlarged and dysfunctional RV (segmental /global) with focal wall motion abnormalities and free wall aneurysm

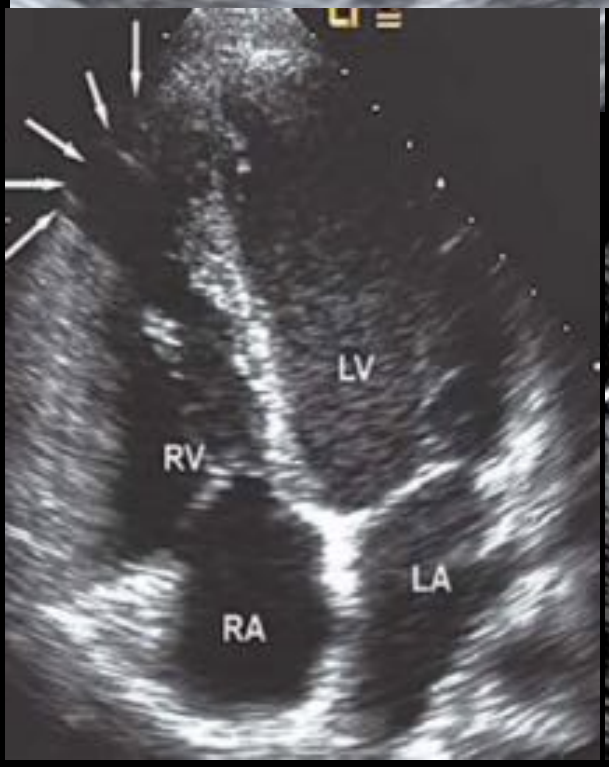
Isolated dilation of RVOT

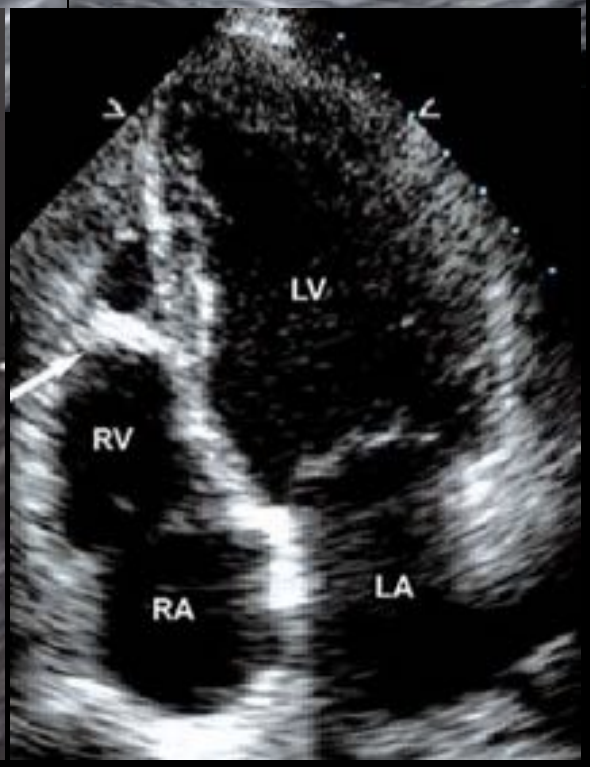
Hyperreflective moderator band

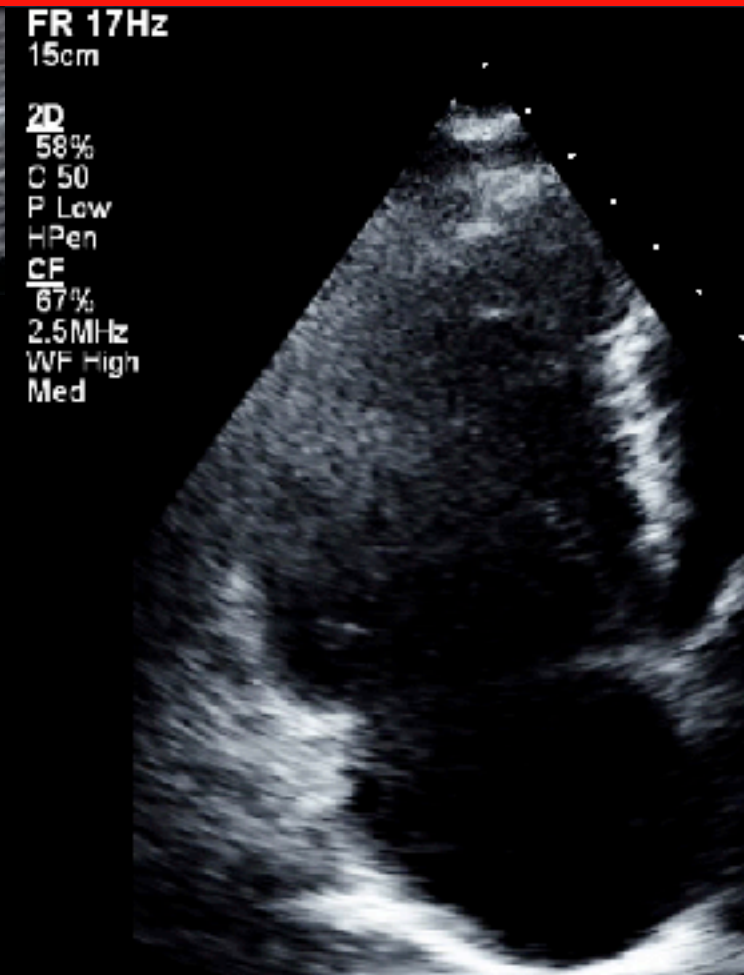
Relative brightness in RV free wall

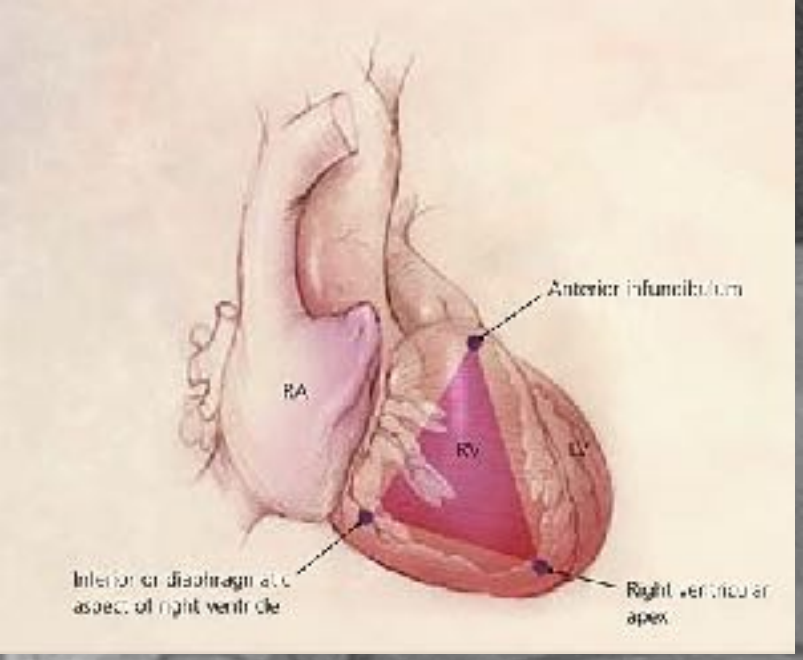











RA
RV
Right ventricular apex

Natural history of ARVC

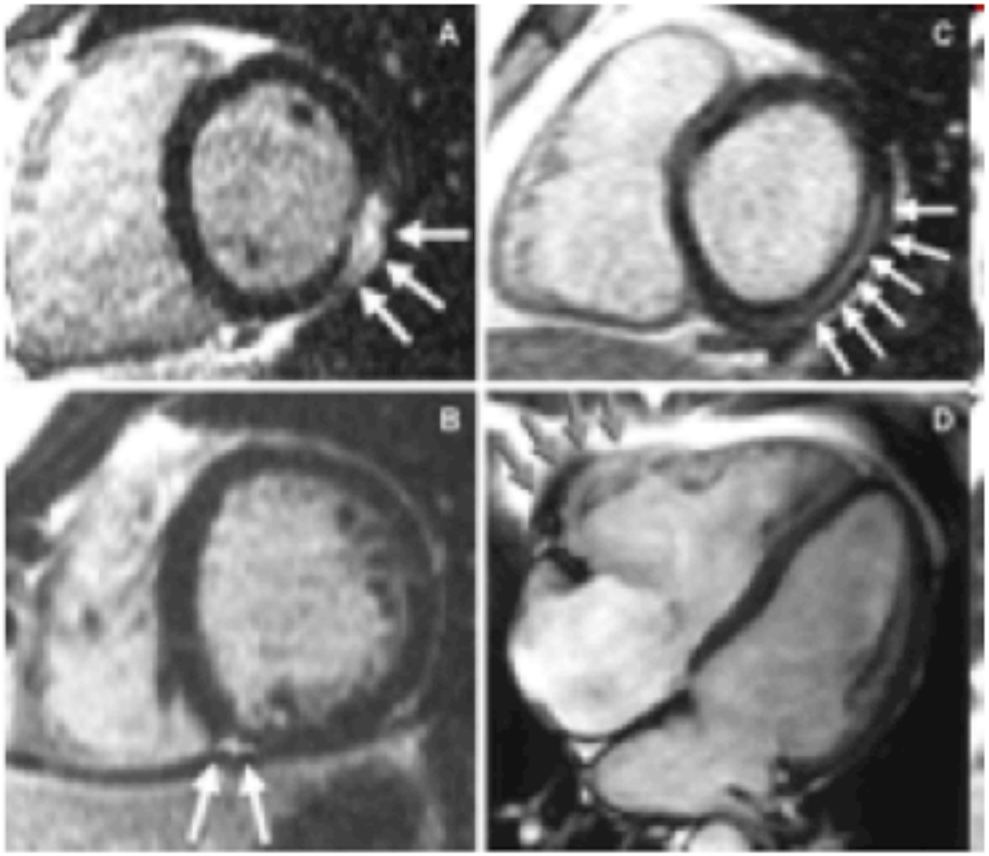
1. Concealed phase

2. Subclinical disease with increased risk of sudden death

3. Overt arrhythmias

4. RV failure which progresses to biventricular disease and refractory heart failure

Left ventricular involvement in ARVC



LV Involvement in 84%

- 77% LV scar by MRI
- 36% LV fat by MRI
- 33% LV dilation
- 27% LV regional wall motion abnormalities
- 15% Reduced LVEF

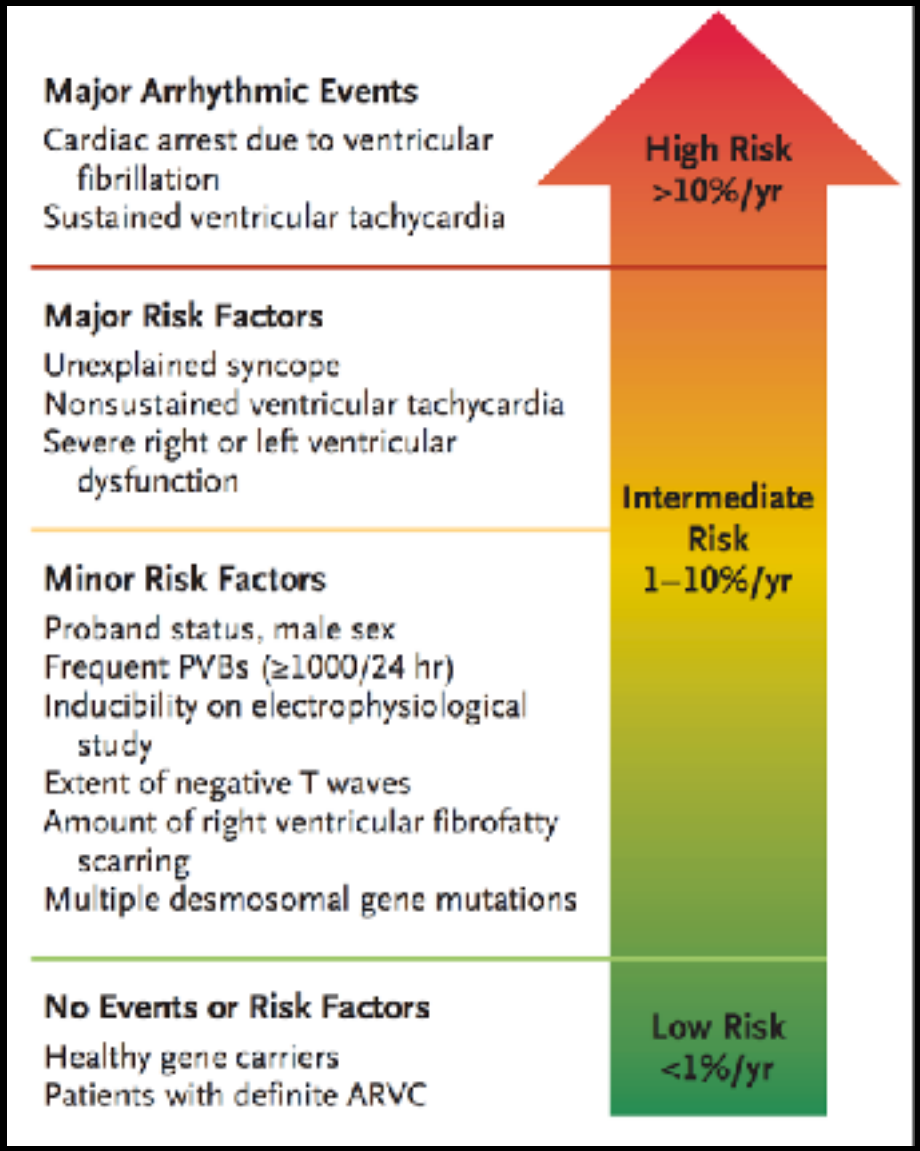
J Am Coll Cardiol 2008;52:2175-87

ARVC : Not always a disease of the RV

- 5% of ARVC patients have predominant LV disease
- Increased representation of DSP mutations
- Clinical features:
  - ECG : T wave inversions in lateral leads
  - Arrhythmia : VT with RBBB morphology
  - Imaging : LV aneurysm and scar

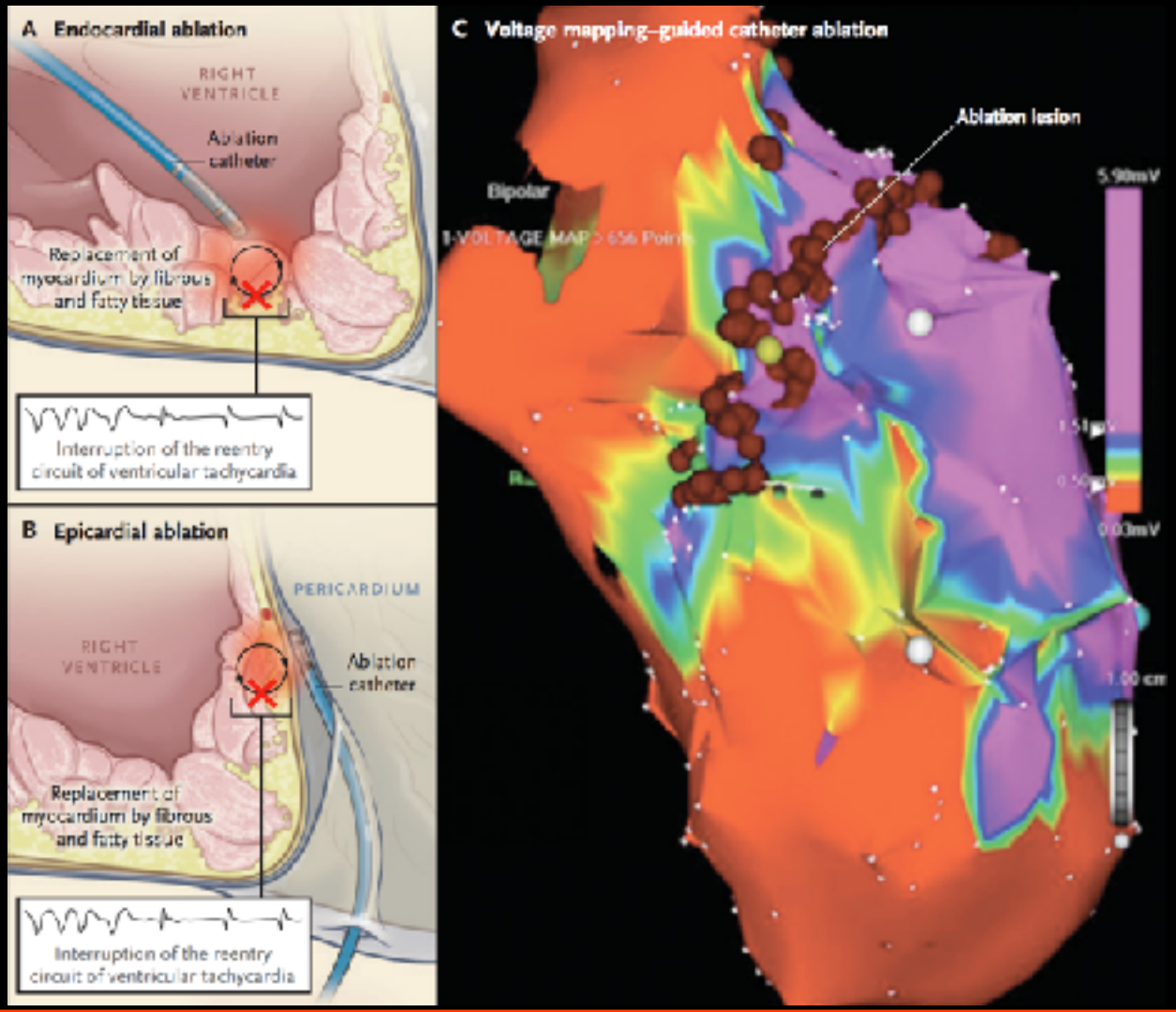
J Am Coll Cardiol 2008;52:2175-87

Prognostic Stratification of Patients with ARVC



N Engl J Med. 2017 Jan 5;376(1):61-72

RFA in ARVC



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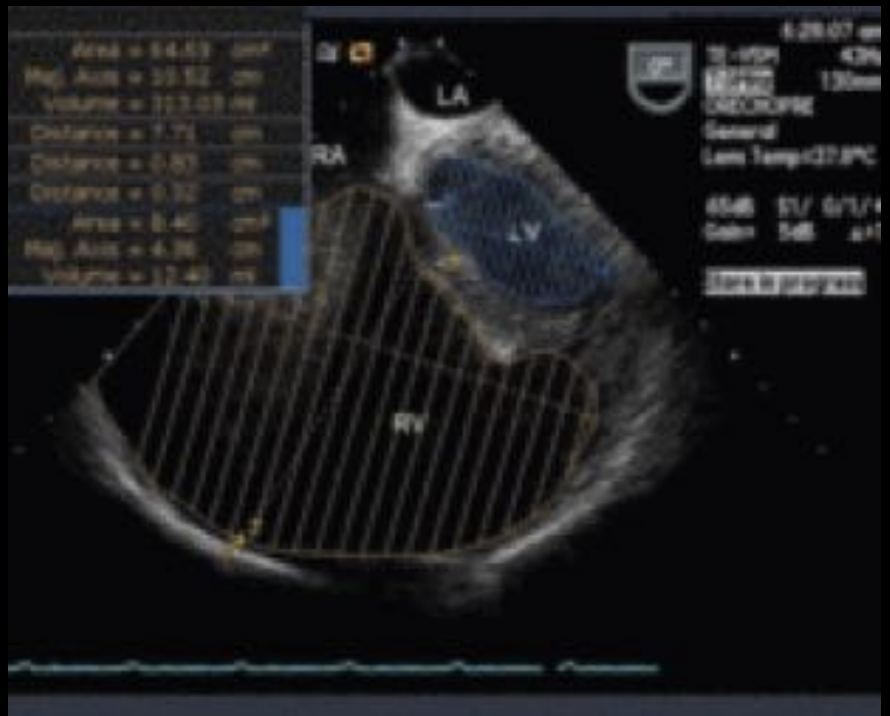
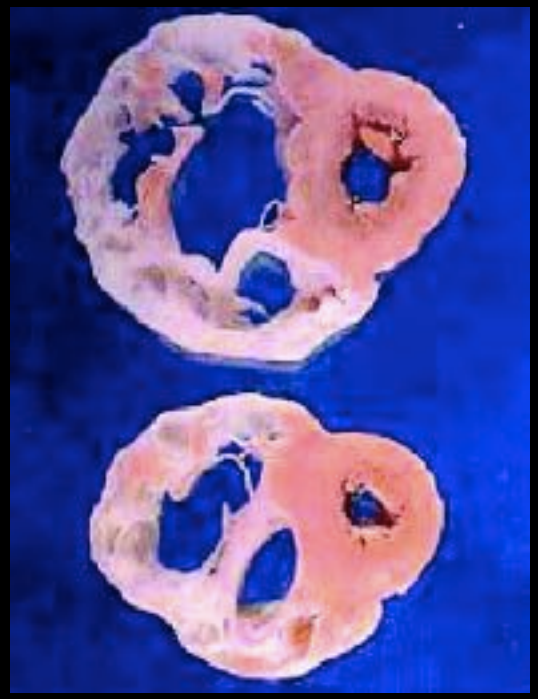
Uhl's anomaly

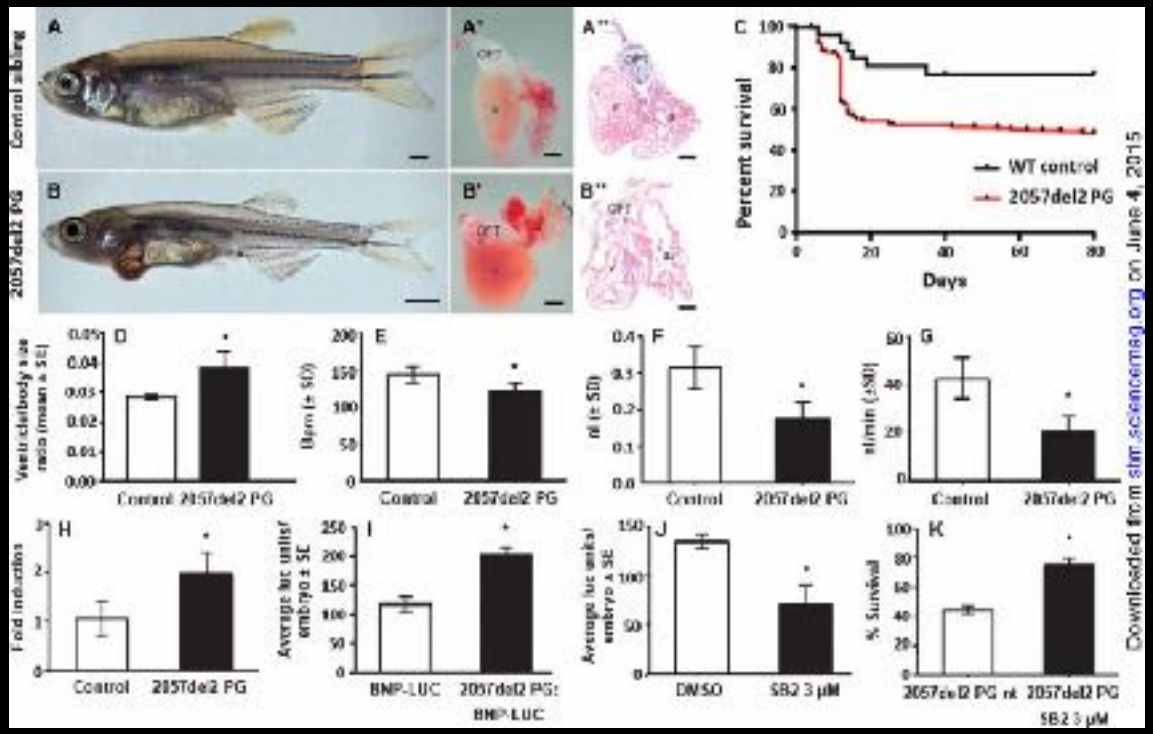
- Complete or partial absence of the myocardium of the RV
- "parchment heart"



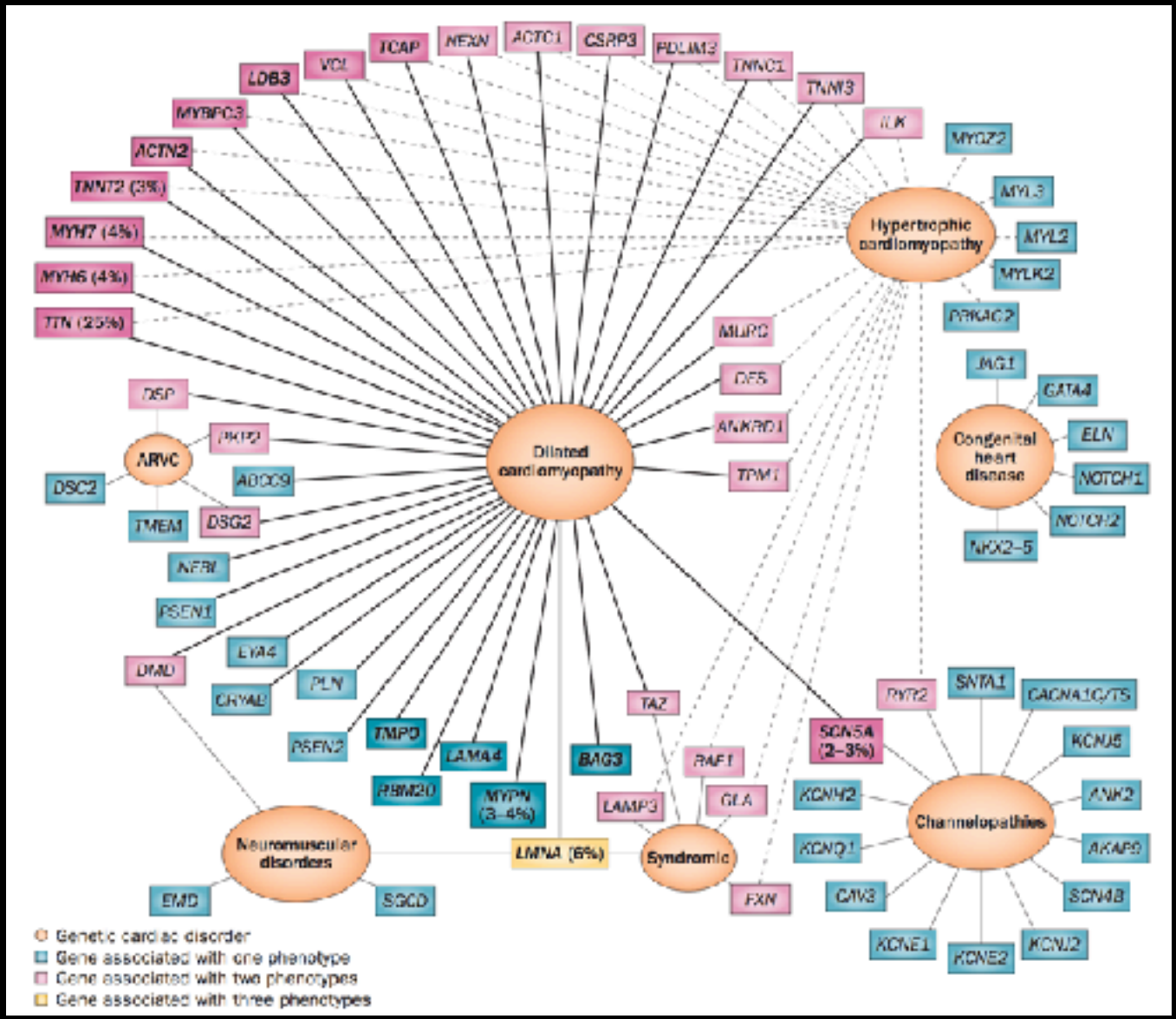


SB216763

- Activator of the Wnt signaling pathway
- In a zebrafish model with defective plakoglobin, this molecule has been shown to prevent or reverse phenotypic manifestations of ARVC



Conclusion


TCAP
NEXN
ACTC1
CSRP3
PDLIM3
TNNC1
TNNI3
LDB3
VCL
MYBPC3
ACTN2
TNNT2 (3%)
MYH7 (4%)
MYH6 (4%)
TTN (25%)
ILK
MYOZ2
MYL3
MYL2
MYLK2
PRKAG2
Hypertrophic cardiomyopathy
MURC
DES
ANKRD1
TPM1
Dilated cardiomyopathy
MGI
GATA4
ELN
NOTCH1
NOTCH2
NKX2-5
Congenital heart disease
DSP
PKP2
ARVC
DSC2
ADD3
TMEM
DSG2
KCNJ
PSEN1
LMO
EYA4
CRYAB
PLN
PSEN2
TMPO
LAMA4
RBM20
MYPN (3–4%)
BAG3
TAZ
LAMP2
RAF1
GLA
FXN
Syndromic
LMNA (6%)
Neuromuscular disorders
EMD
SGCD
RYR2
SNTA1
CACNA1C/TS
SCN5A (2–3%)
KCNJ5
KCNH2
ANK2
KCNQ1
AKAP9
CAV3
SCN4B
KCNE1
KCNE2
KCNJ2
Channelopathies
Genetic cardiac disorder
Gene associated with one phenotype
Gene associated with two phenotypes
Gene associated with three phenotypes