Cardiac Involvement in Children with Mitochondrial Disease

Lucy Youngmin Eun, MD, Young-Mock Lee, MD

Pediatric Cardiology, Pediatric Neurology
Heart Center, Gangnam Severance Hospital
Yonsei University Health System, Seoul, Korea

Disclosure

I have no financial conflicts of interest
to disclose concerning this presentation.

Mitochondria

- Prevalence : 1 / 10~15,000
- DNA mutation : more than hundreds of different pathogenic mitochondrial DNA mutations in humans
- Oxidative phosphorylation defects
- Activity of mitochondrial enzymes : decreased

Mitochondria

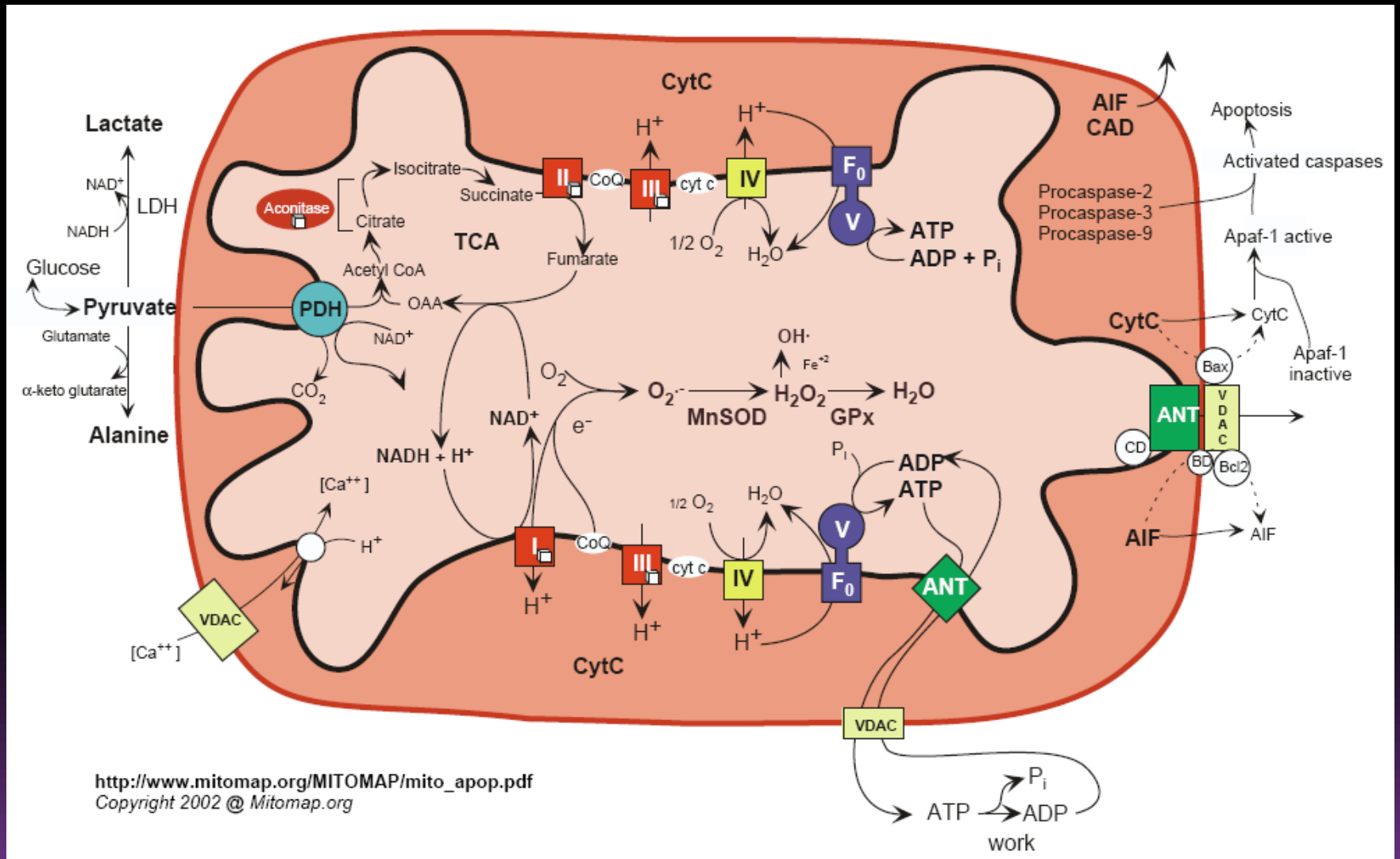

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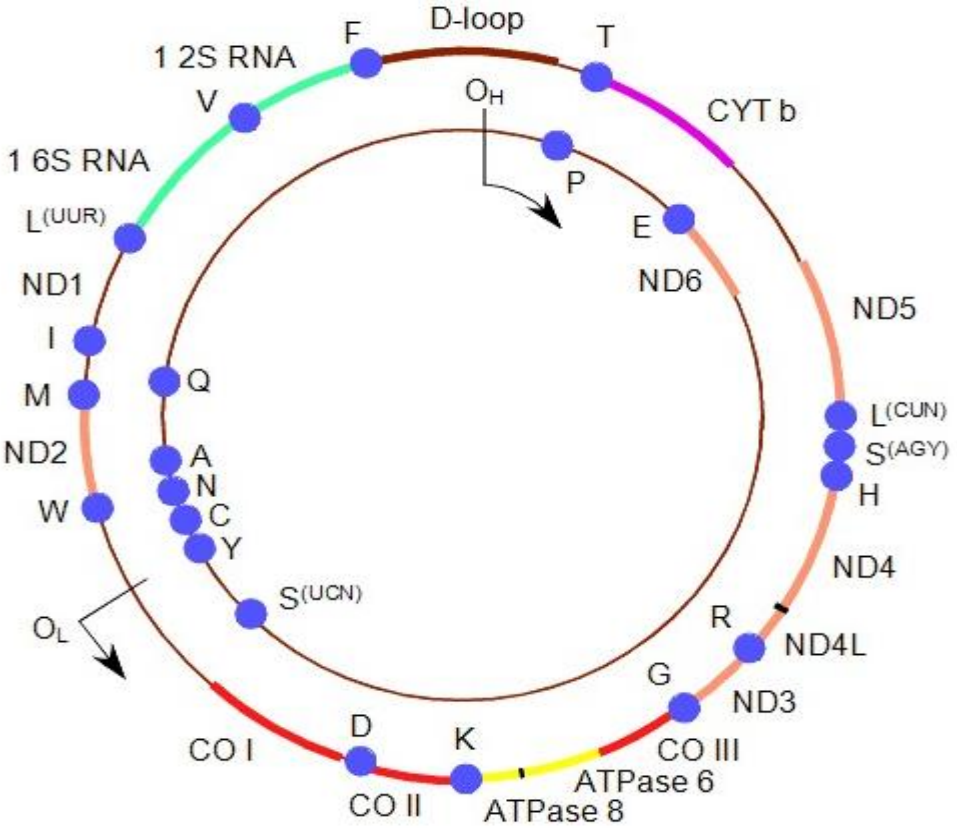
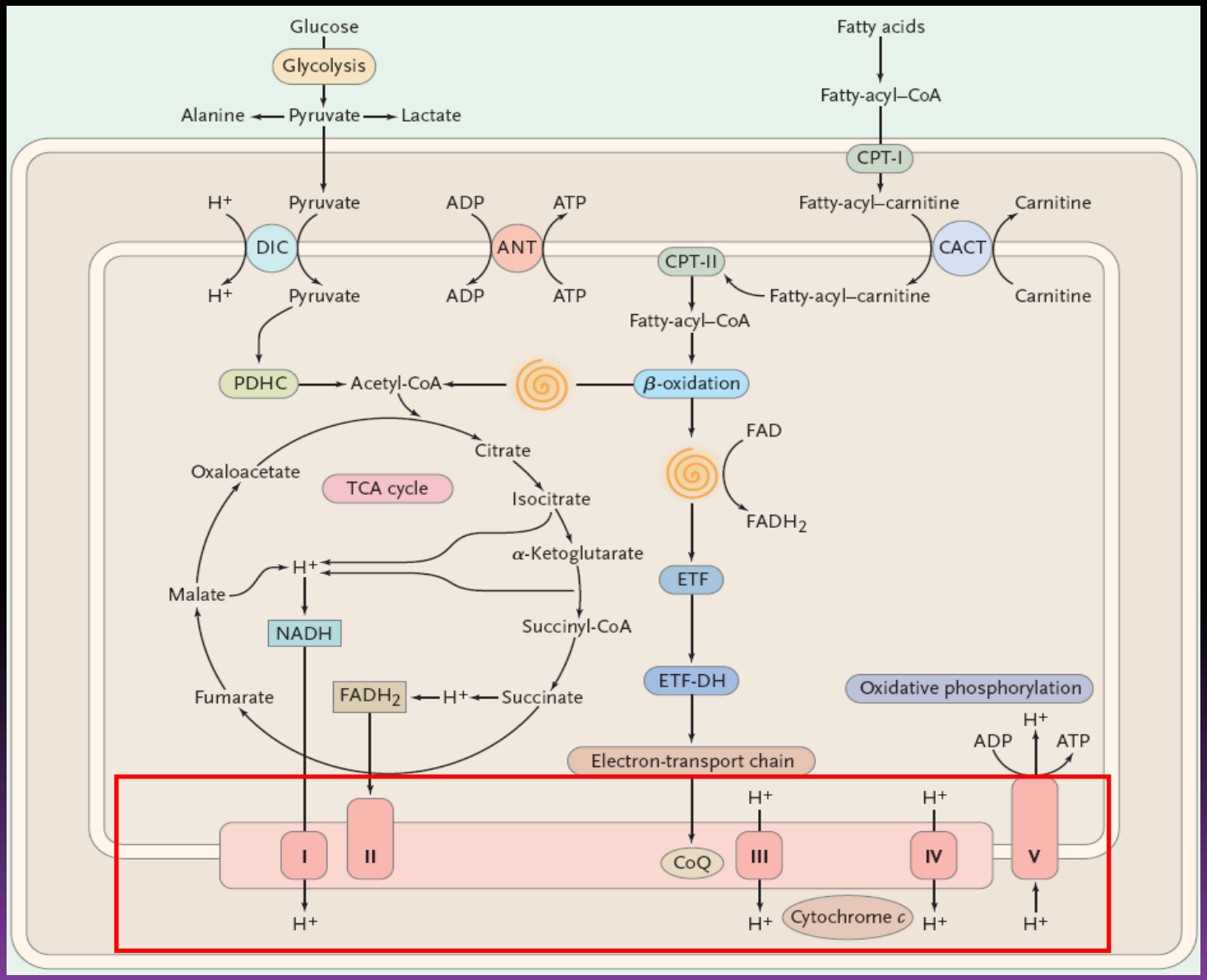
Diagram of the mammalian mitochondrion showing the relationship between energy production, ROS generation, and regulation of apoptosis.

Mitochondria

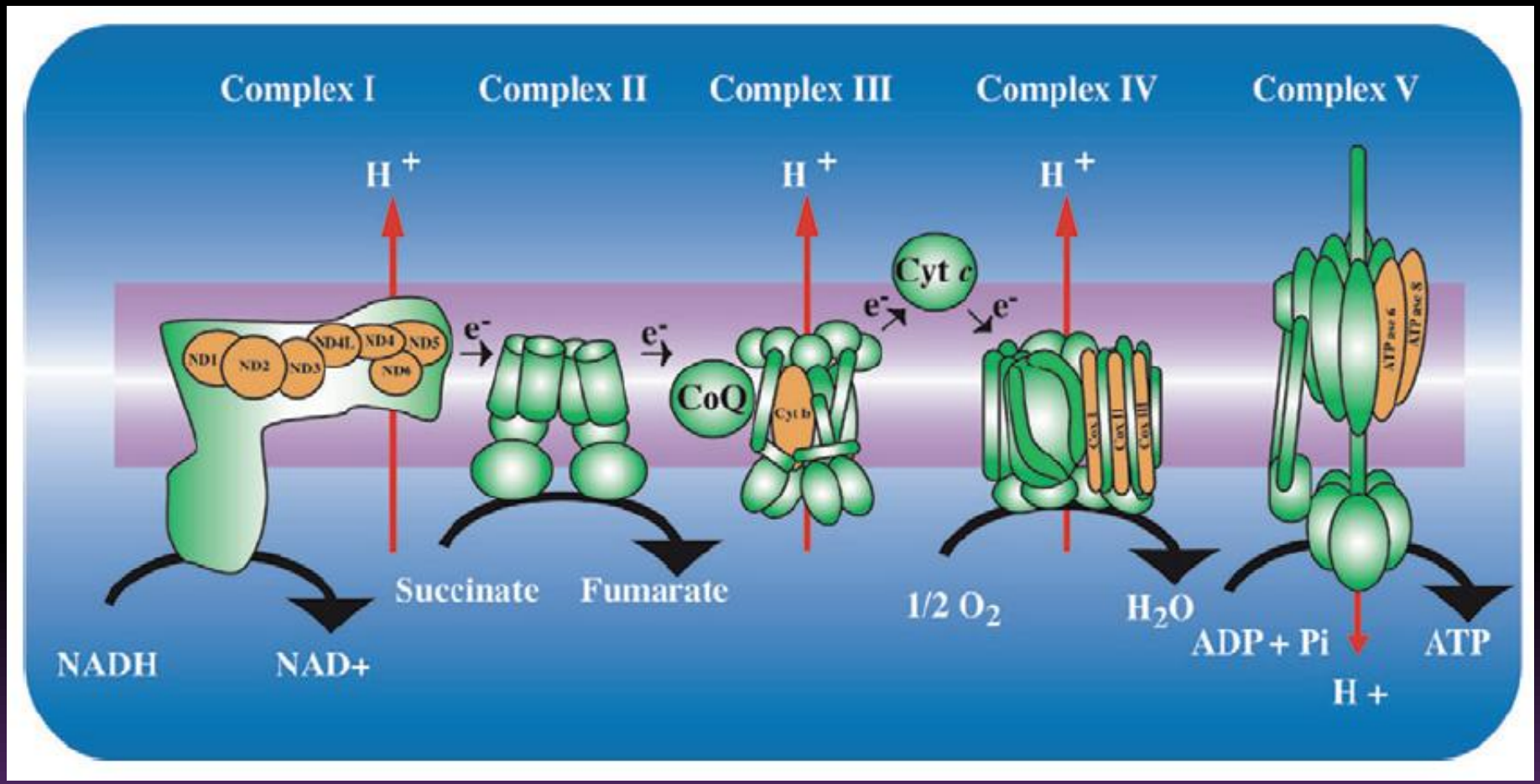


CO = cytochrome oxidase (COX) subunit genes
CYT b = cytochrome b
ND = complex I subunit genes
O_H = origin of heavy strand replication
O_L = origin of light strand replication
D-loop = non-coding displacement loop or control region

Respiratory Chain Complex

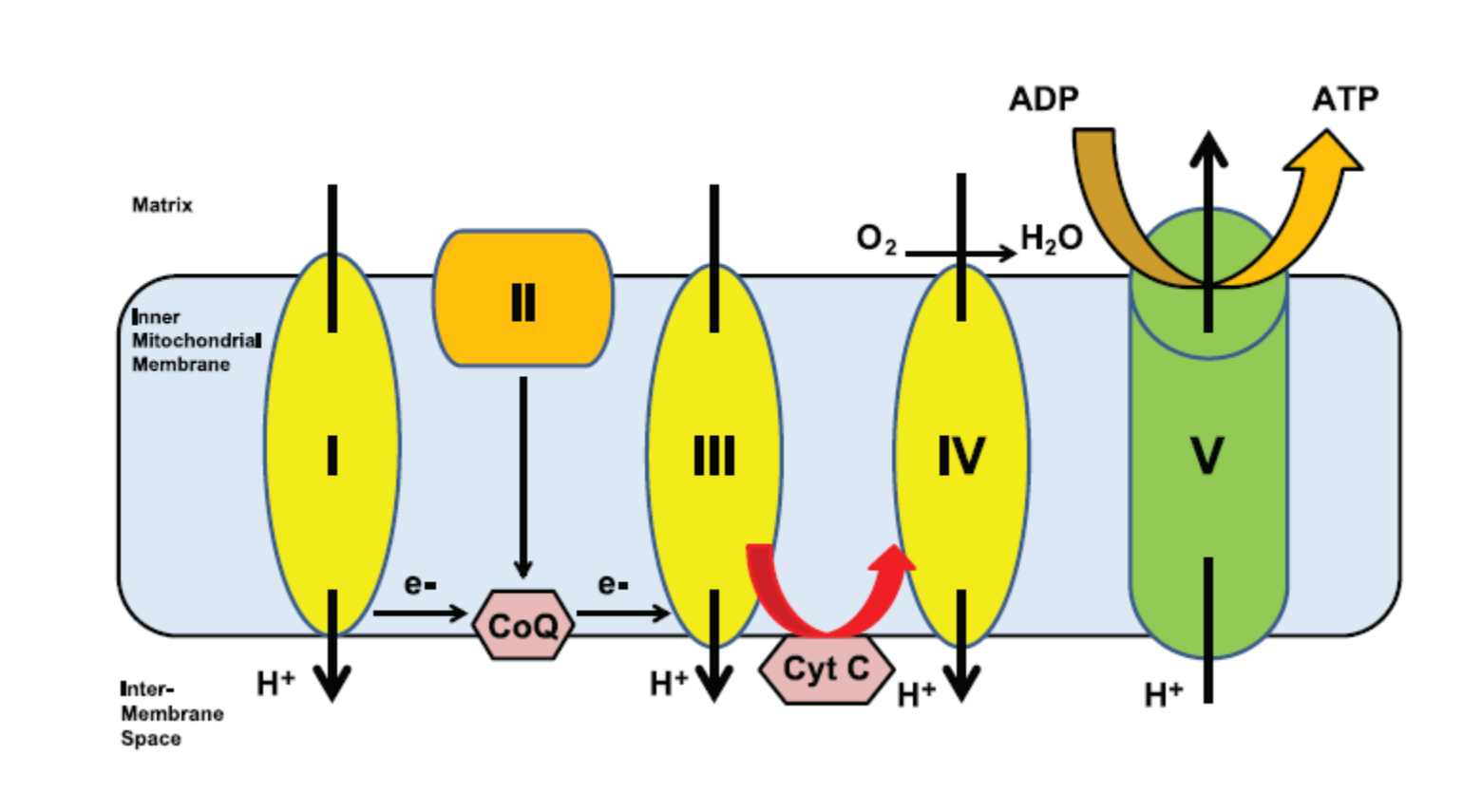


Oxidative Phosphorylation

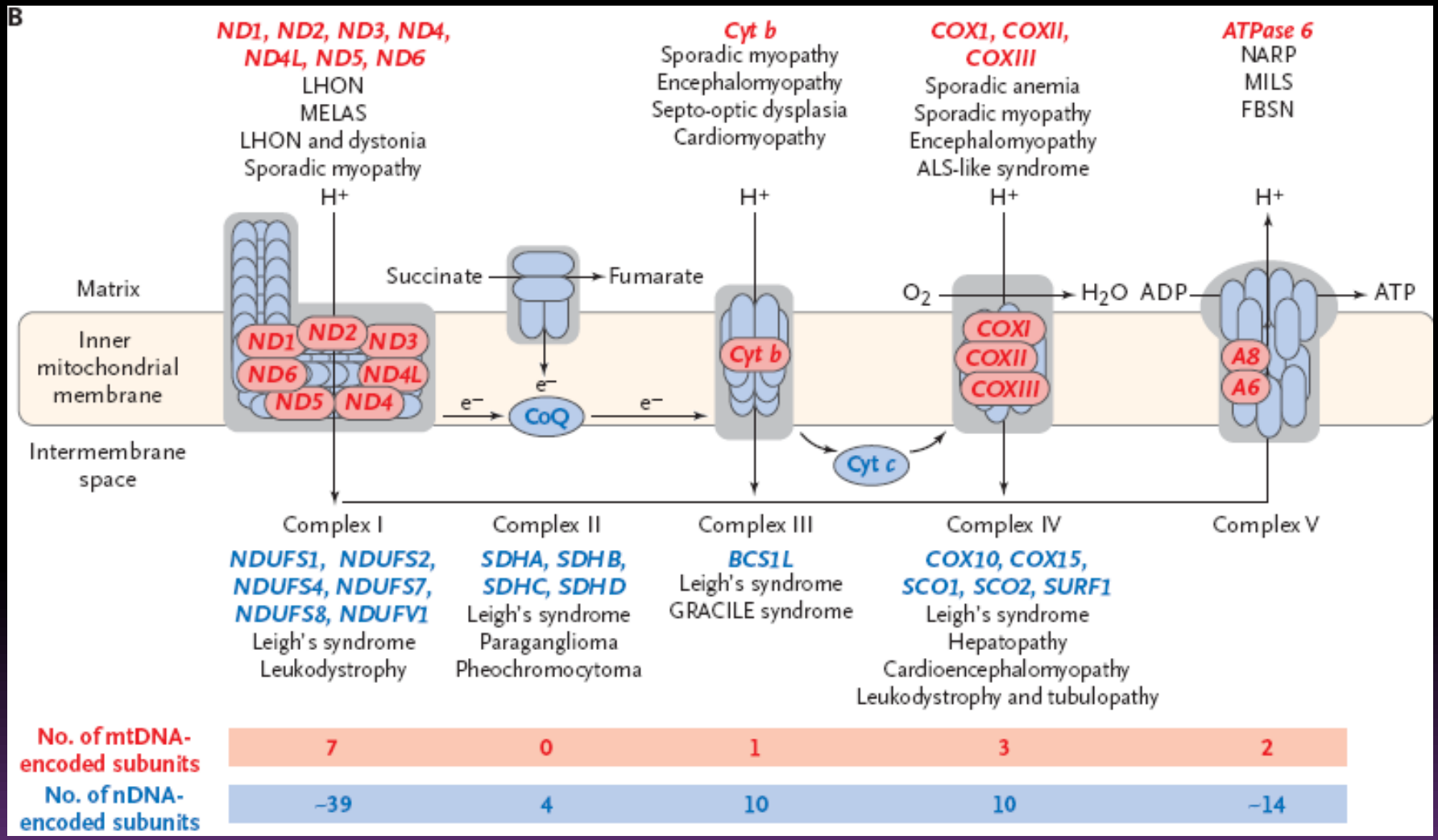


Definition of Mitochondrial Disease

Mitochondrial Disease

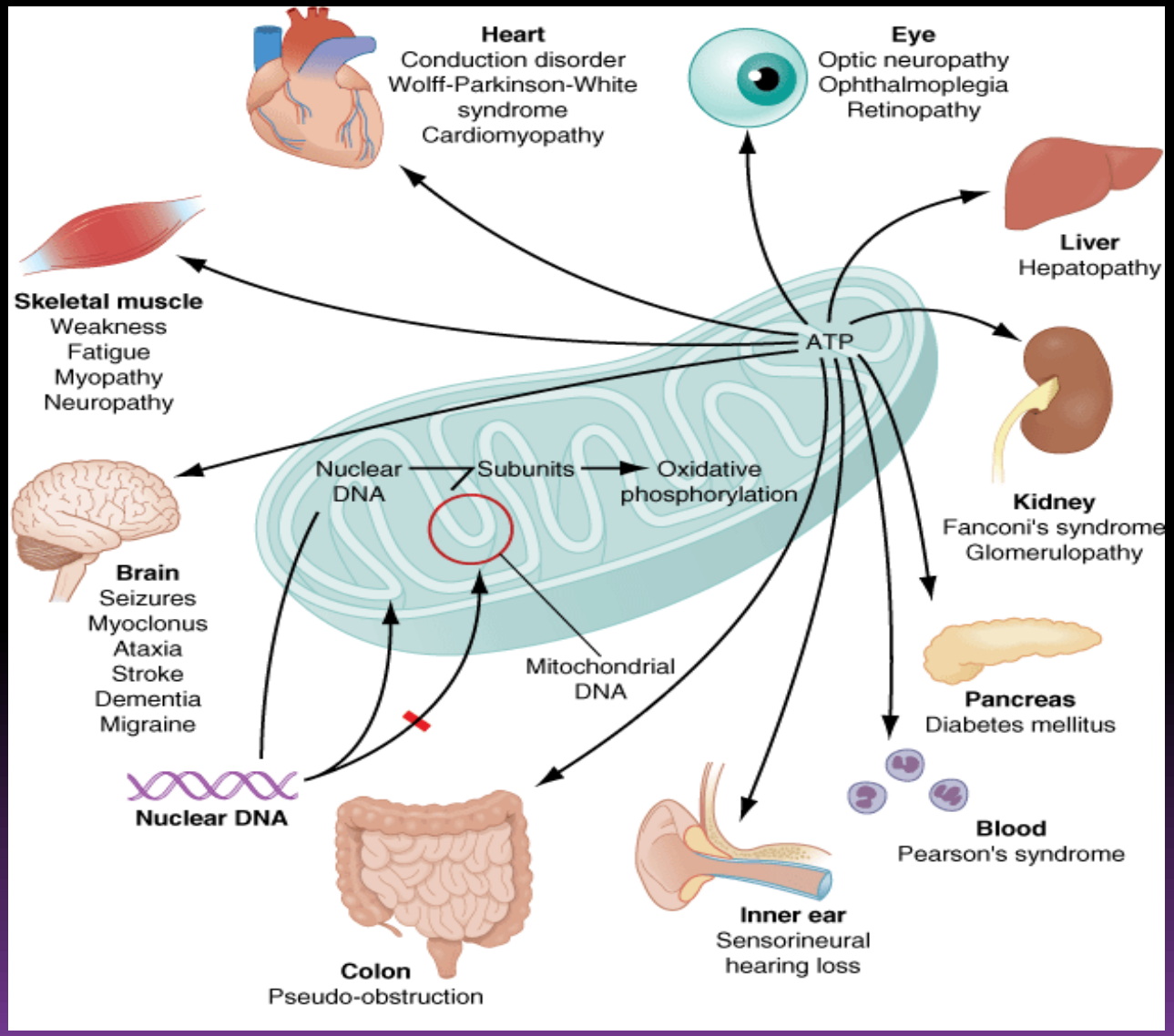


Mitochondria



NEJM 2003

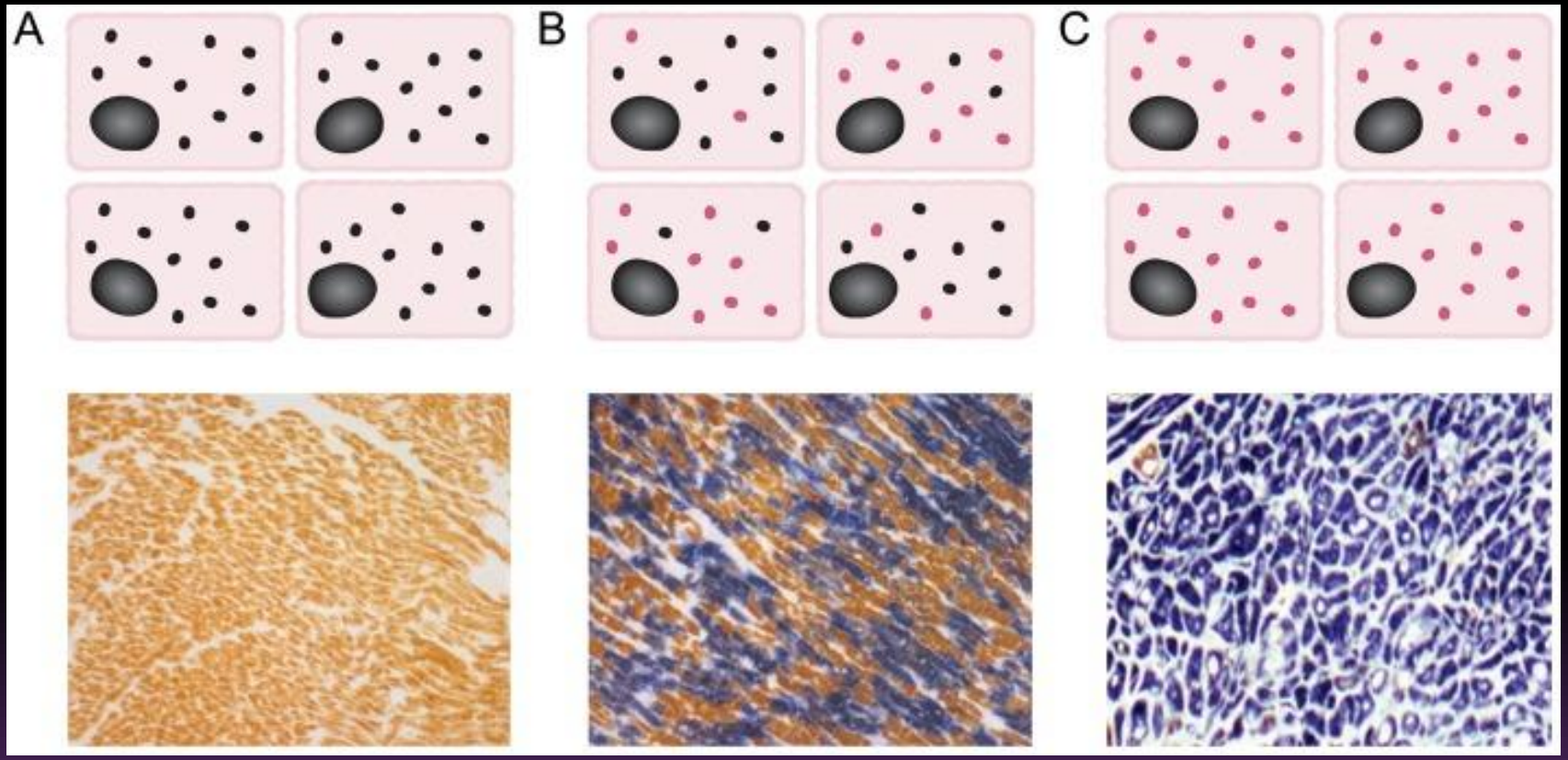
Organs Involvement



Cardiac Involvement

- Oxidative phosphorylation defects
- Cardiac involvement : 33 %
- Cardiomyopathy : 5.6 %
- Activity of mitochondrial enzymes : decreased
- Myocardial biopsy : absolute increase of the number and size of mitochondria
- Mitochondrial proliferation in cardiomyocyte

What Happen to Cardiomyocytes..?



Cardiovascular Manifstations

TABLE II. Mitochondrial Syndromes and Their Cardiovascular Manifestations

Syndrome	Cardiovascular Manifestations
Barth syndrome (lethal infantile cardiomyopathy)	Dilated cardiomyopathy and left ventricular hypertrabeculation
Chronic progressive external ophthalmoplegia	Arrhythmia
Leigh syndrome (subacute necrotizing encephalomyelopathy)	Cardiomyopathy and arrhythmia
Kearns-Sayre syndrome	Arrhythmia
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes	Dilated cardiomyopathy and left ventricular hypertrabeculation
Myoclonic epilepsy and ragged red fibers	Cardiomyopathy and arrhythmia
Maternally inherited diabetes and deafness	Left ventricular hypertrabeculation and arrhythmia
Neurogenic muscle weakness, ataxia, and retinitis pigmentosa	Cardiomyopathy
Maternally inherited Leigh syndrome	Cardiomyopathy

Meyers DE et al. Tex Heart Inst J 2013;40(4):385-94

Mitochondria

Table 2 Cardiac phenotypes associated with pathogenic mtDNA mutations

		Electropathy		Cardiomyopathy				
Gene	mtDNA mutation	Ventricular pre-excitation	Conduction disease	Hypertrophic	Dilated	Restrictive	Left ventricular non-compaction	Histiocytoid
Common								
MTTL1	m.3243A>G	++	+	++	+	+	+	−
MTTI	m.4300A>G	−	−	++	+	−	−	−
MTTK	m.8344A>G	++	+	++	++	−	−	+
MTND4	m.11778G>A	++	−	+	−	−	−	−
	single, large-scale mtDNA deletion	−	++	−	+	−	−	−
Rare								
MTRNR1	m.1555A>G	−	−	−	−	+	−	−
MTTV	m.1624C>T	−	−	+	+	−	−	−
MTTL1	m.3252T>C	−	+	−	+	−	−	−
	m.3260A>G	+	−	+	+	−	−	−
	m.3303T>C	−	+	+	+	−	−	−
MTND1	m.3337G>A	−	−	+	+	−	−	−
	m.3460G>A	+	−	+	−	−	+	−
MTTI	m.4269A>G	−	−	−	+	−	−	−
	m.4277T>C	−	−	+	−	−	−	−
	m.4284G>A	−	+	+	+	−	−	−
	m.4317A>G	−	−	+	+	−	−	−
	m.4320C>T	−	−	+	−	−	−	−
MTTK	m.8363G>A	−	−	+	+	−	−	−
MTATP8/	m.8528T>C	−	−	+	−	−	−	−
MTATP6	m.8529G>A	−	−	+	−	−	−	−
MTATP6	m.8993T>G	−	−	+	−	−	−	−
MTTG	m.9997T>C	−	−	+	−	−	−	−
MTND4	m.11778A>G	−	−	−	+	−	−	−
MTTL2	m.12297T>C	−	−	−	+	−	−	−
MTND5	m.13513G>A	+	+	−	−	−	−	−
MTND6	m.14484T>C	−	−	−	+	−	−	−
MTCYB	m.14849T>C	−	−	+	−	−	−	−
	m.15498G>A	−	−	−	−	−	−	+

Pathogenic mitochondrial DNA mutations were identified from a search of online databases,[18,19] together with the cumulative experience of the authors, excluding rare single nucleotide polymorphisms, and haplogroup markers. mtDNA, mitochondrial DNA; ++, reported in cross-sectional cohort study with ≥10% frequency; +, reported in single case report(s)/family series only; −, not reported.

Bates MG et al. Eur **Heart** J. (2012) ;33:3023-33

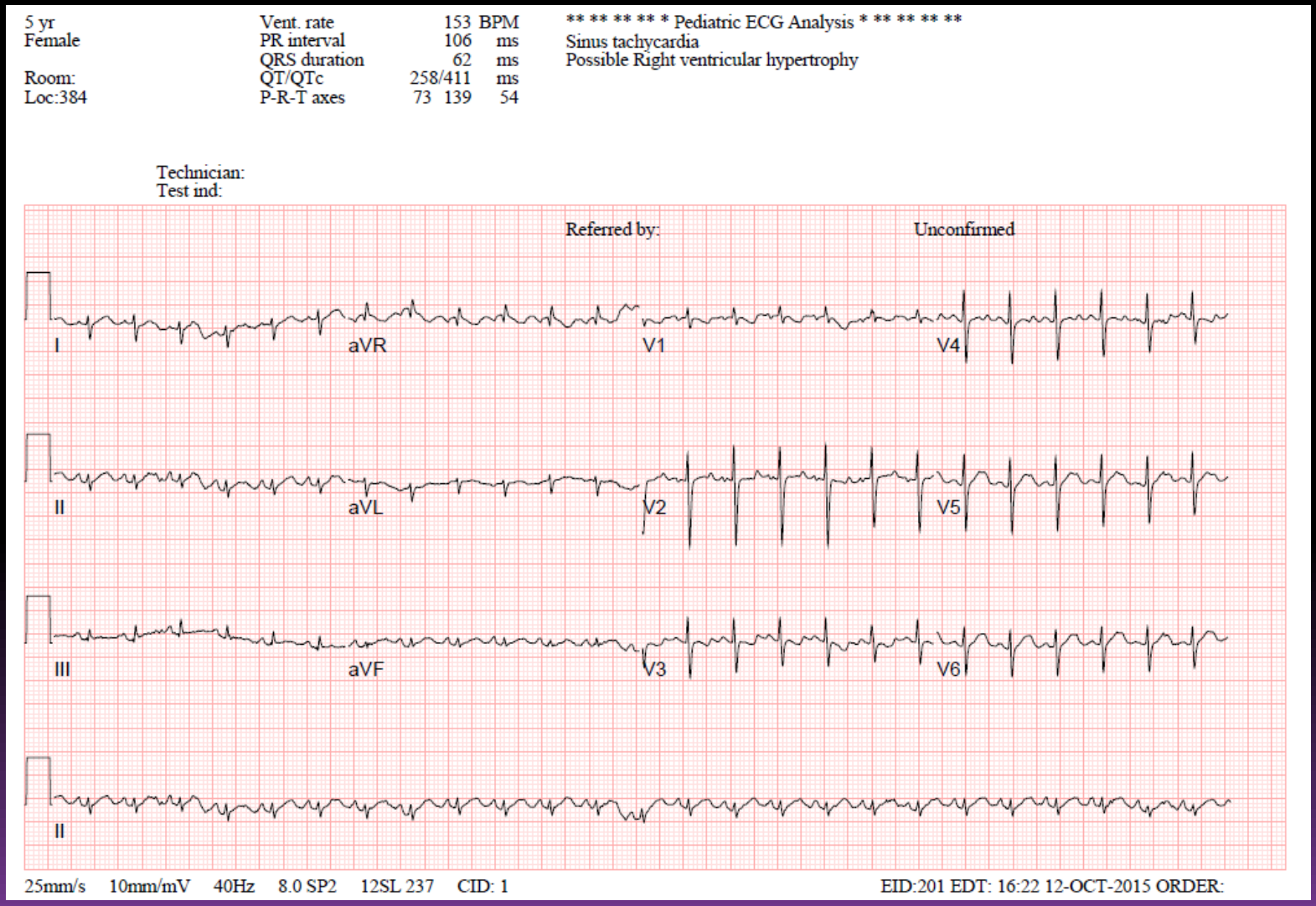
Rhythm

- arrhythmia; tachycardia, bradycardia
- conduction abnormalities;
- isolated ST-segment depression in two or more contiguous leads;
- isolated inverted T-waves;
- pathologic Q-waves;
- a Sokolow-Lyon index > 35 mm as sign of LV hypertrophy

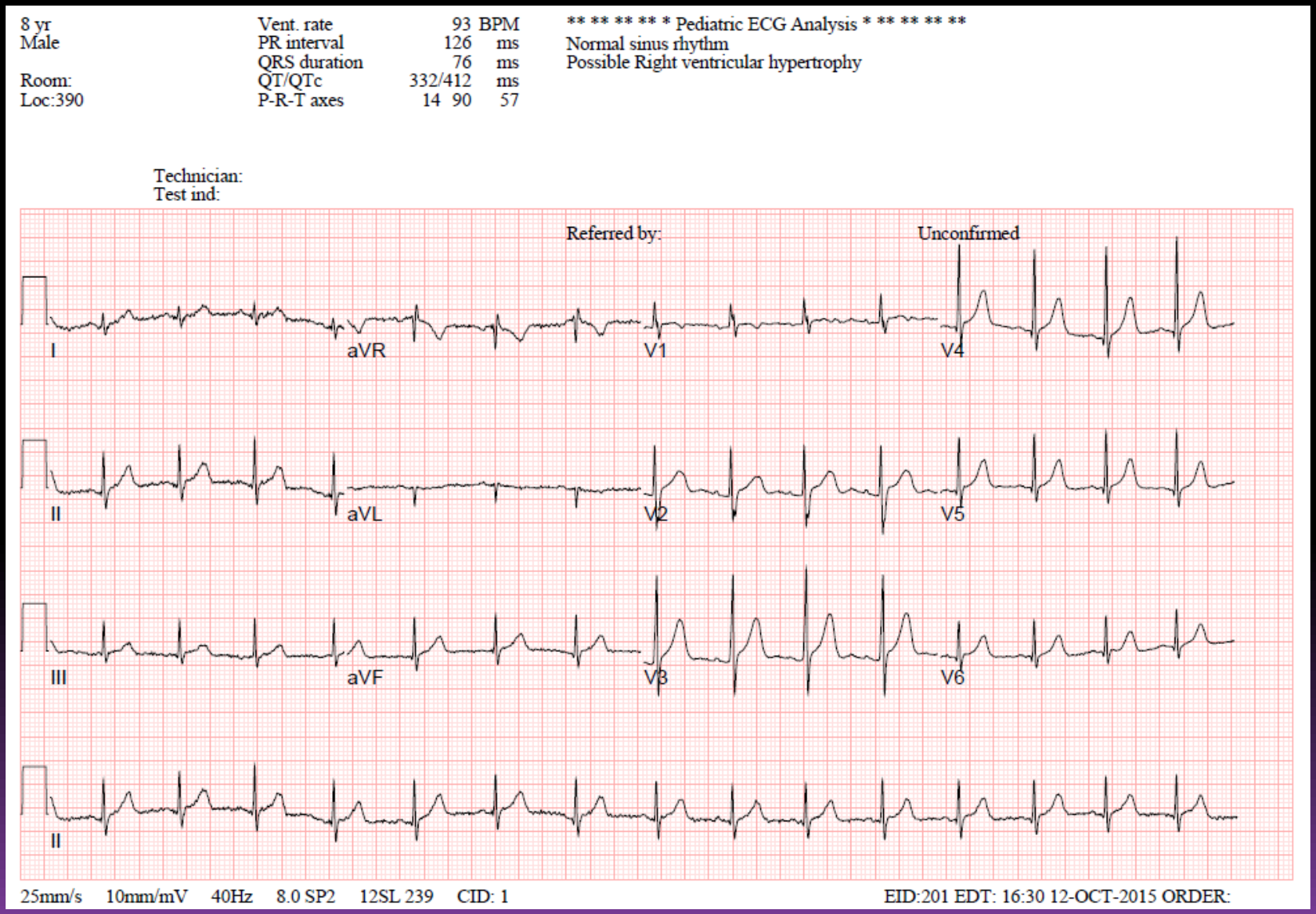
Conduction

- Kearns-Sayre syndrome
  - progressive heart block
  - ophthalmoplegia
  - degenerative retinopathy
  - renal tubular dysfunction
  - delayed growth
  - short stature
  - slow mental neurologic deterioration

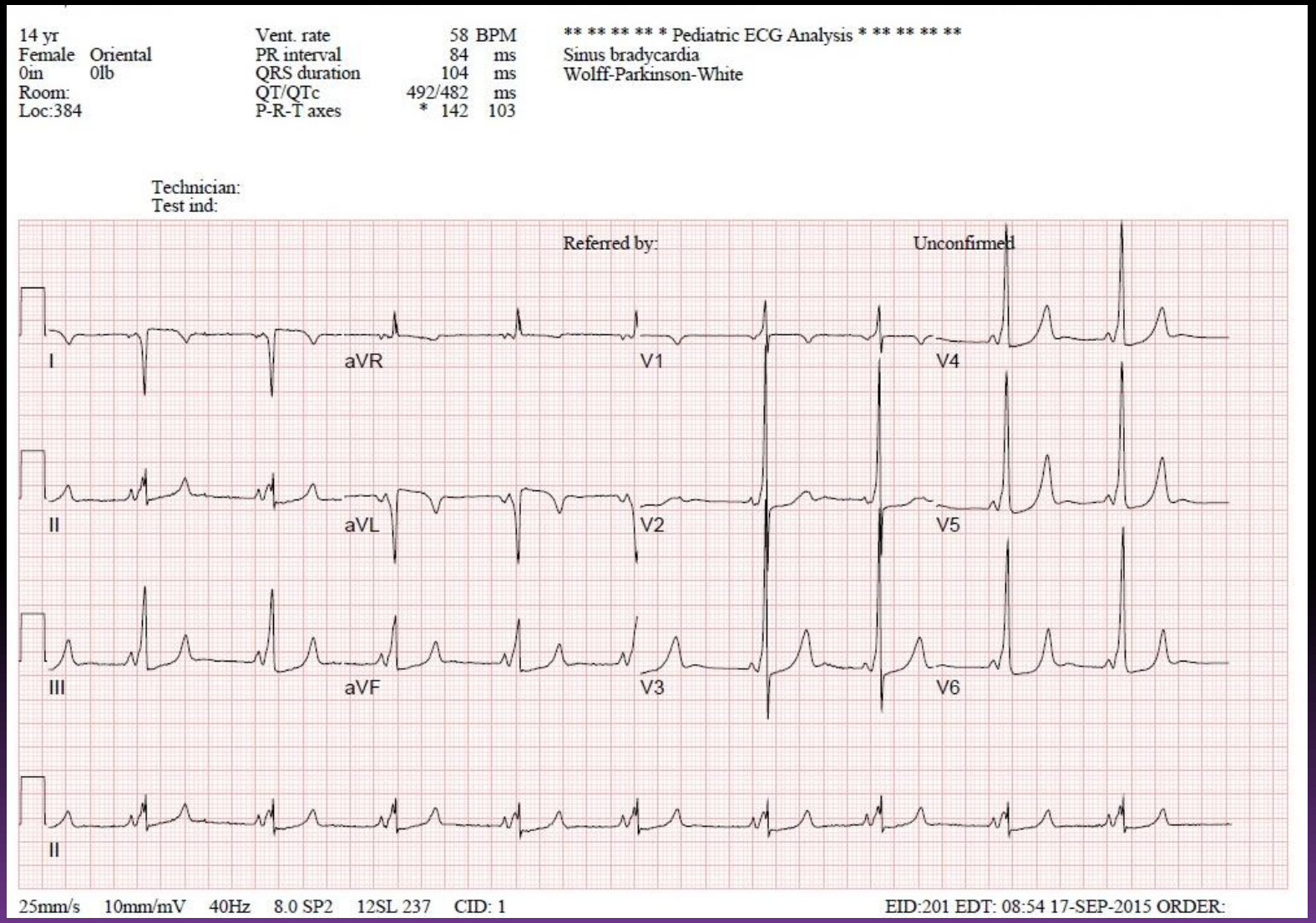
Rhythm : F/5 year



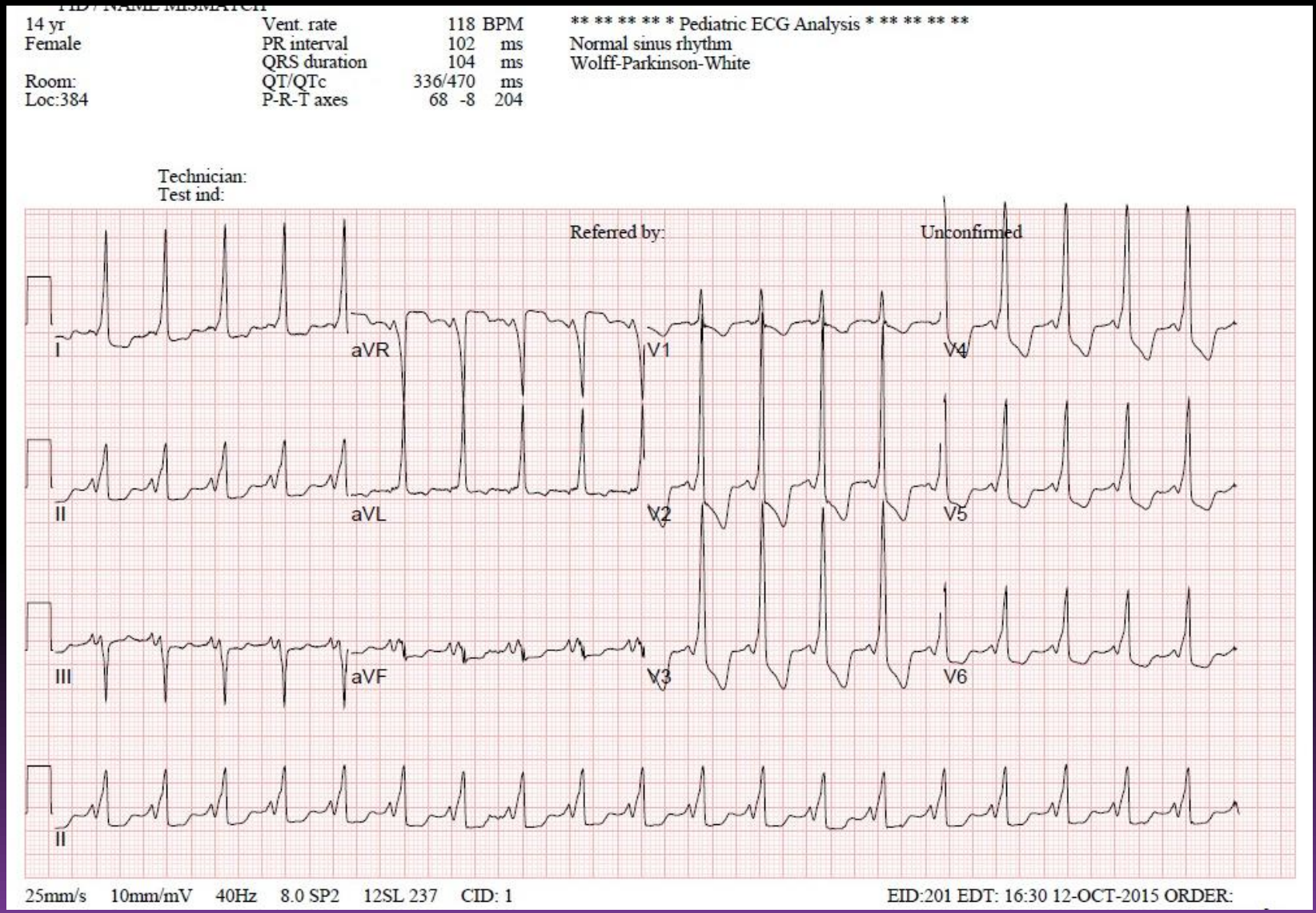
Rhythm : M/8 year



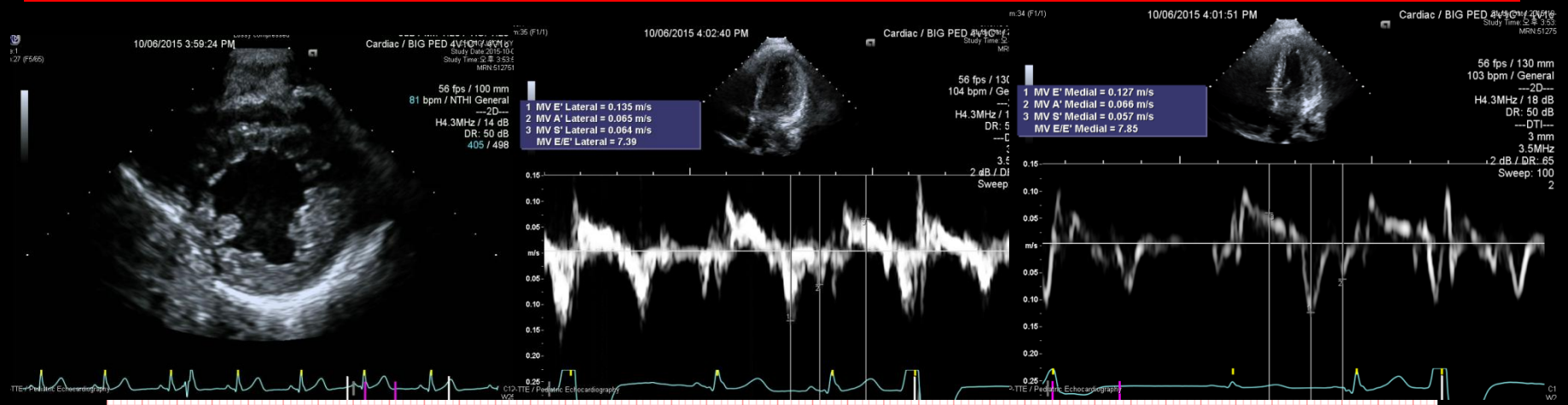
Rhythm : F/14 year

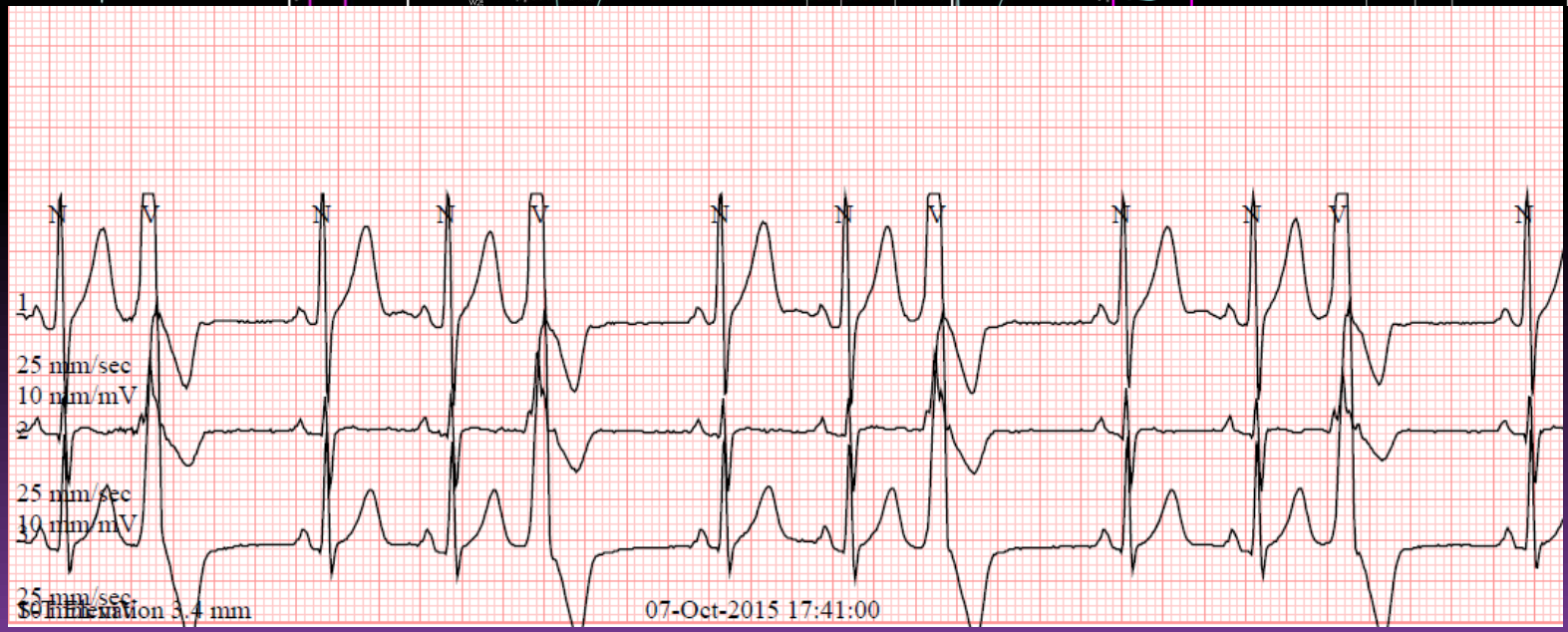


Rhythm : F/14 year



Case : M/12 year





Laboratory

- total creatine kinase (CK)
- troponin T (TnT)
- brain natriuretic-peptide (NT-proBNP)

Myocardial Involvement

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Restrictive cardiomyopathy
- Unclassified cardiomyopathy :

  LV hyper-trabeculation / non-compaction

  Takotsubo syndrome

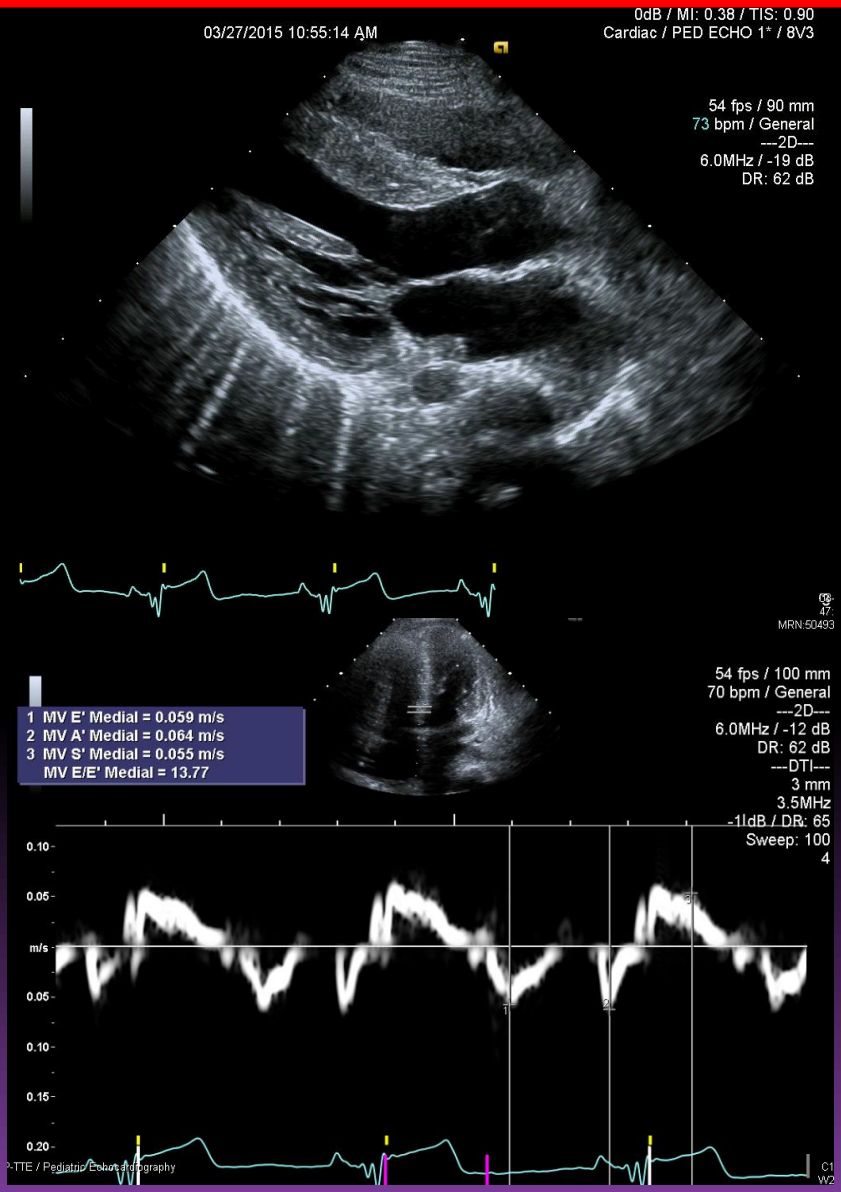
Hypertrophic Cardiomyopathy

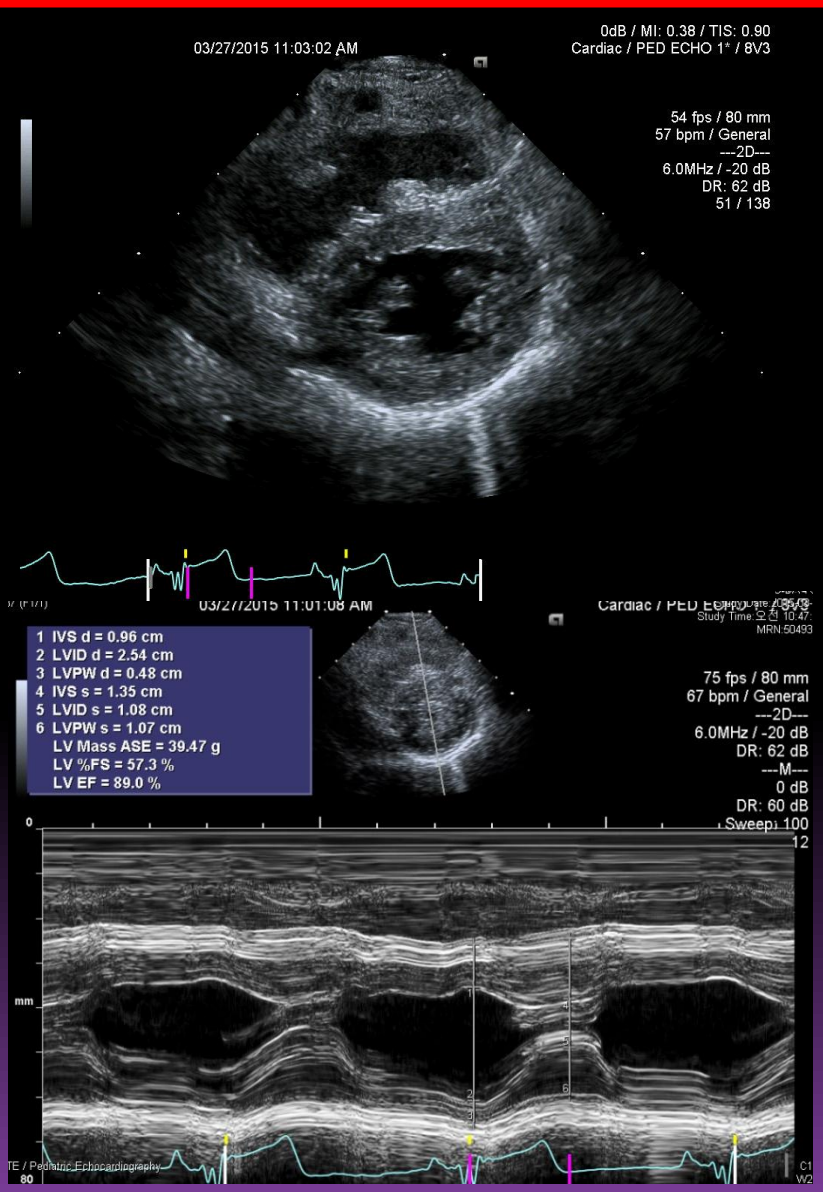
- Hypertrophic remodeling
  : dominant pattern --- around 40 %
- Characteristics
  Rarely observed LVOT obstruction
  Higher progression to heart failure
  ventricular dilatation
  impaired systolic function

Hypertrophic Cardiomyopathy

- Cytochrome c oxidase coenzyme deficiency
- Cytochrome c oxidase deficiency
- Cytochrome c oxidase deficiency with histiocytoid cardiomyopathy
- Hereditary HDM with mitochondrial myopathy of skeletal muscle and cataracts
- HCM with Leigh disease (subacute necrotizing encephalomyelopathy)

MELAS CMP : F/10yr





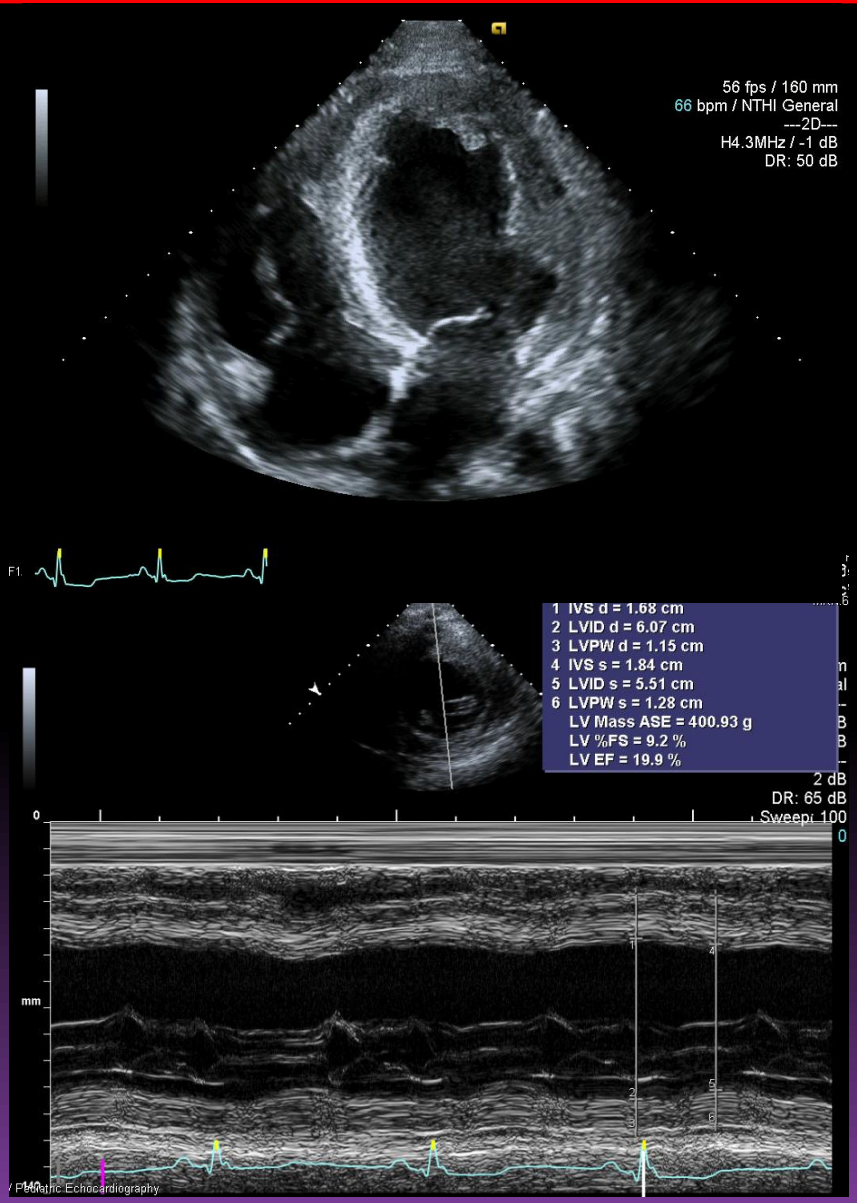
Dilated Cardiomyopathy

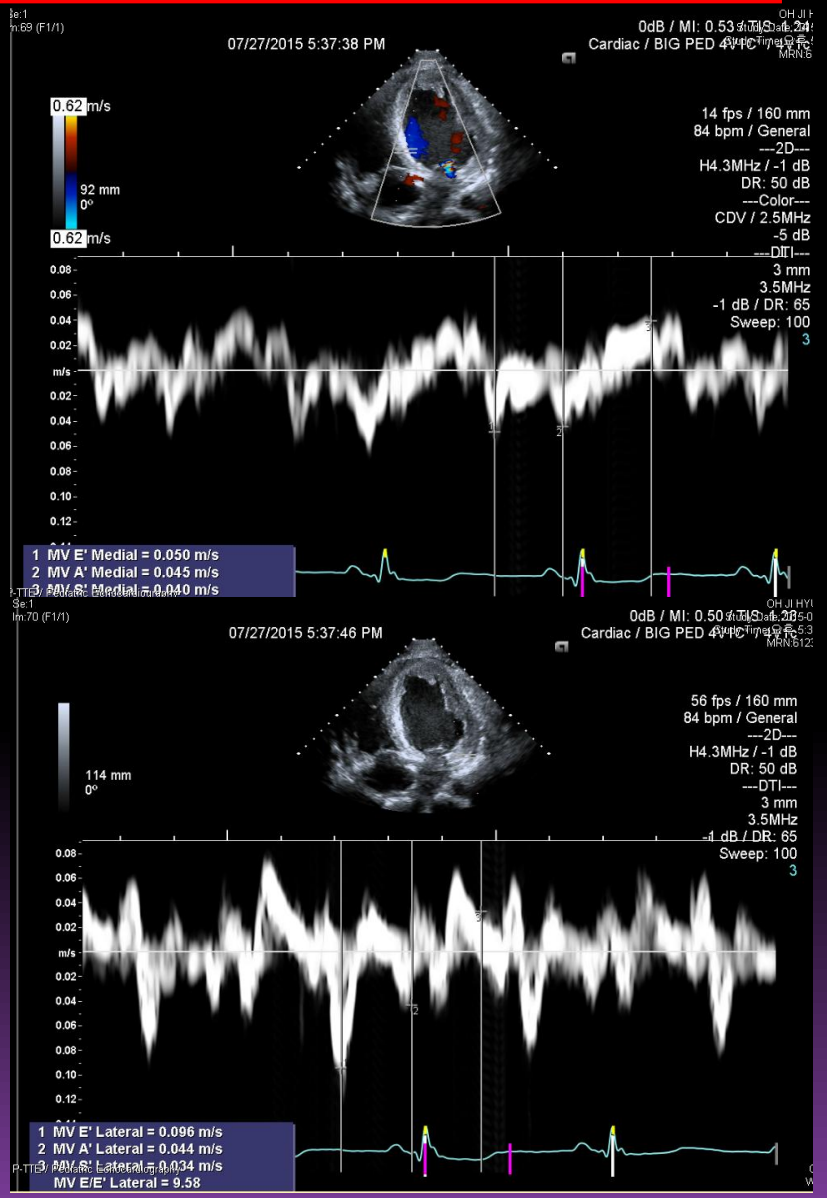
- More commonly represents progression of pre-existing hypertrophy with chamber dilation and systolic dysfunction
- Symptom : limited – skeletal myopathy
- Progression of DCM may be slow
- Responsive to heart failure therapy

Dilated Cardiomyopathy

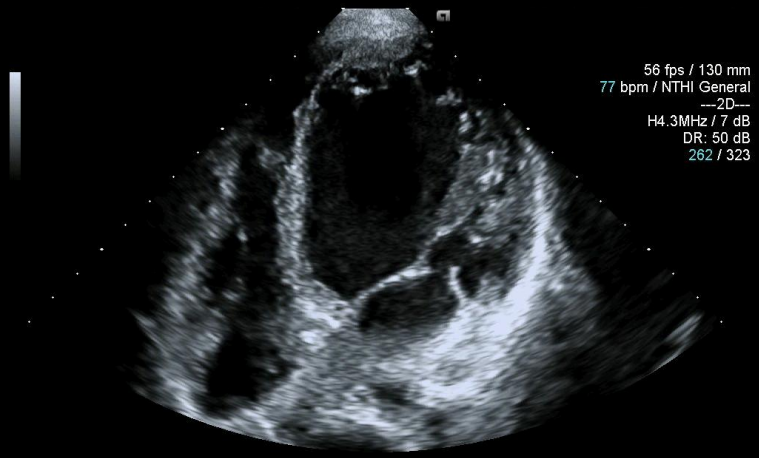
- X-linked cardiomyopathy with abnormal mitochondrial myopathy, granulocytopenia
- MELAS : mitochondrial encephalopathy, lactic acidosis, and stroke
- MERRF syndrome : myoclonic epilepsy and ragged red fibers
- Barth syndrome : 3-methylglutaconic acidemia

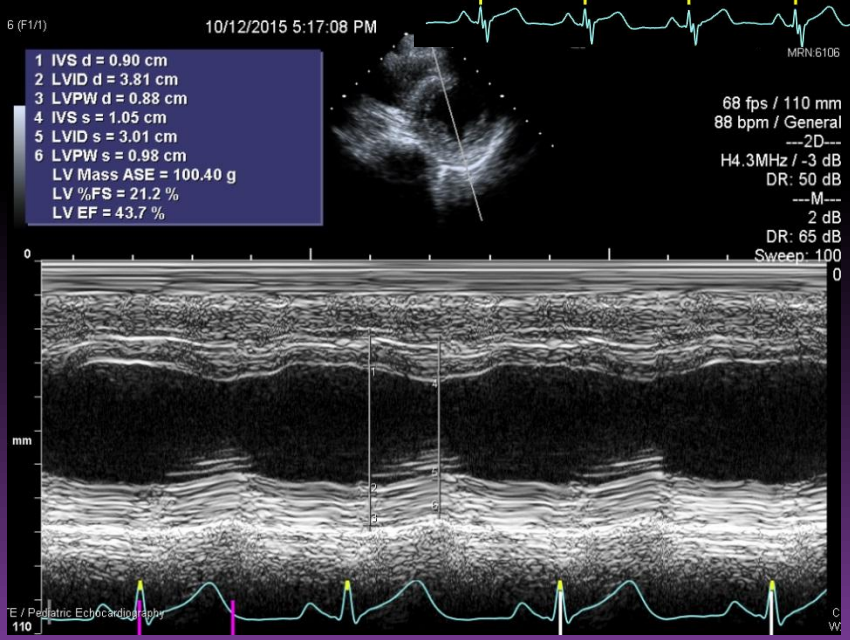
MELAS CMP : M/22yr

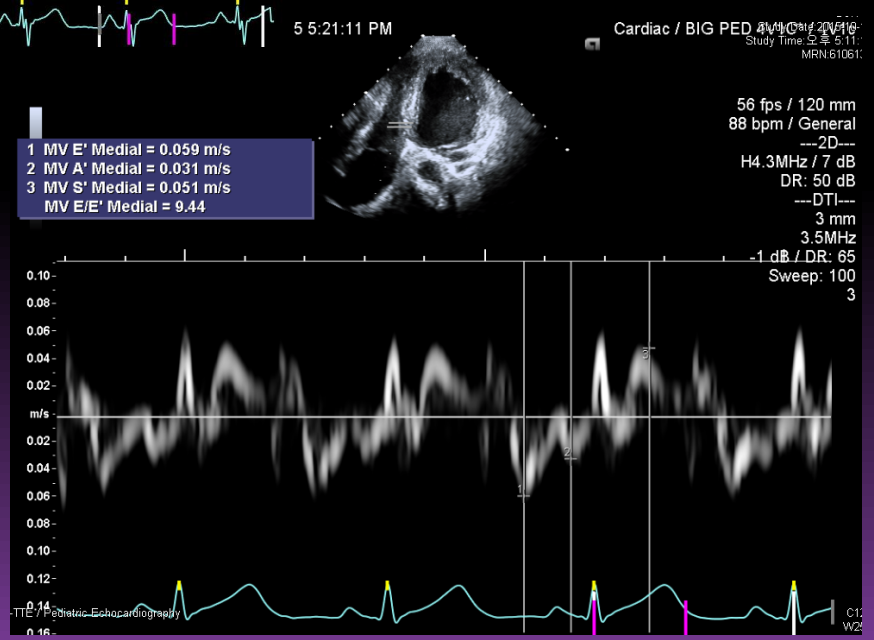




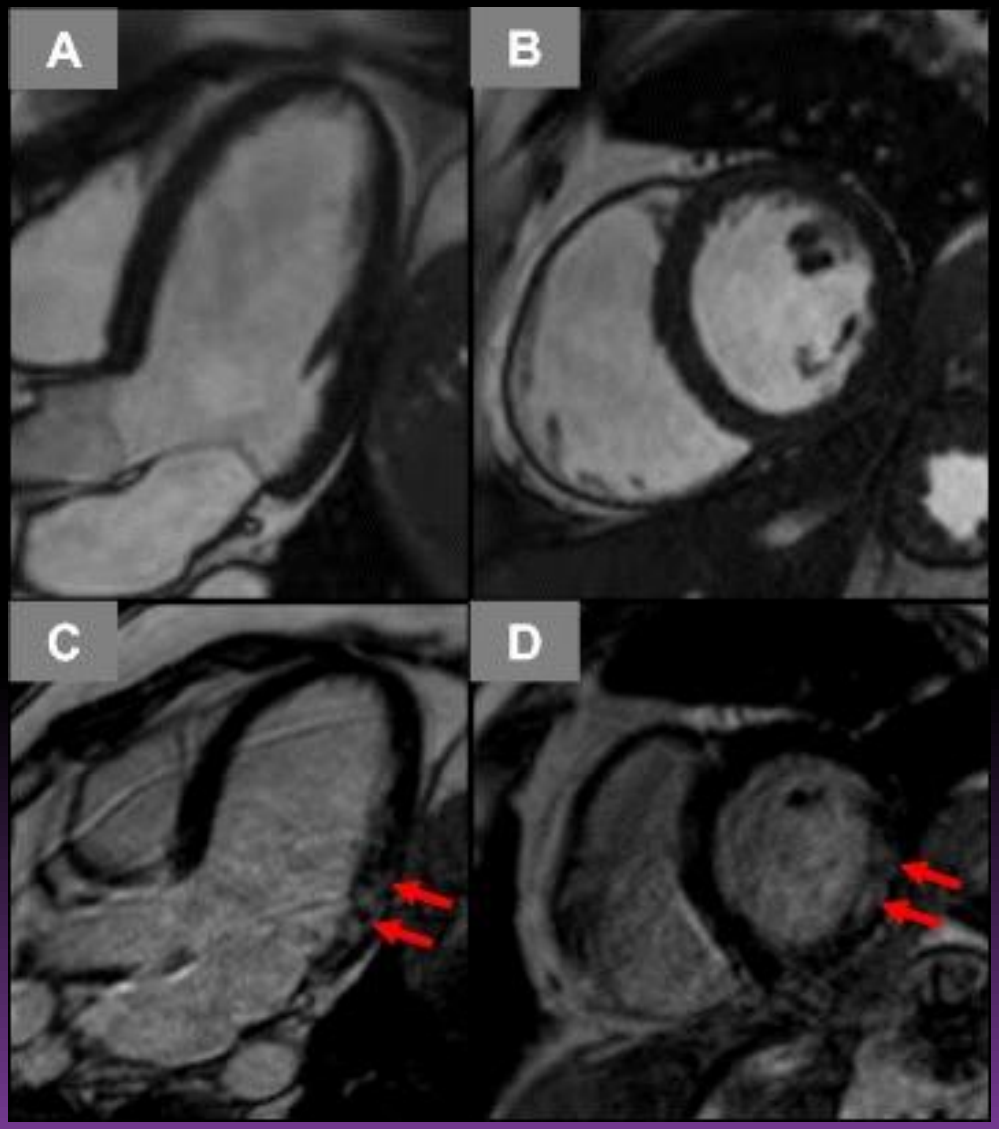
MELAS CMP : M/16yr



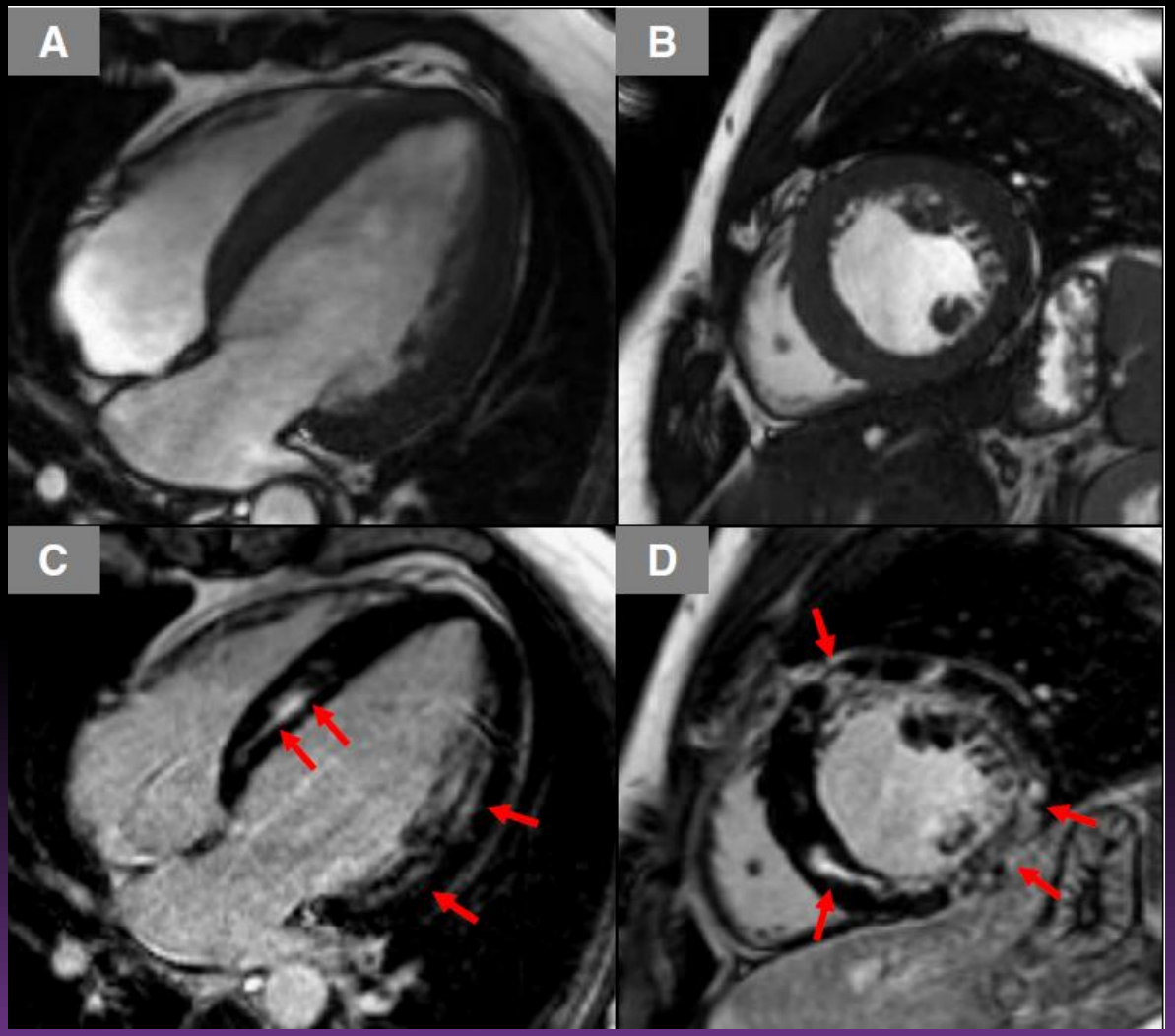




MELAS CMP : M/17yr

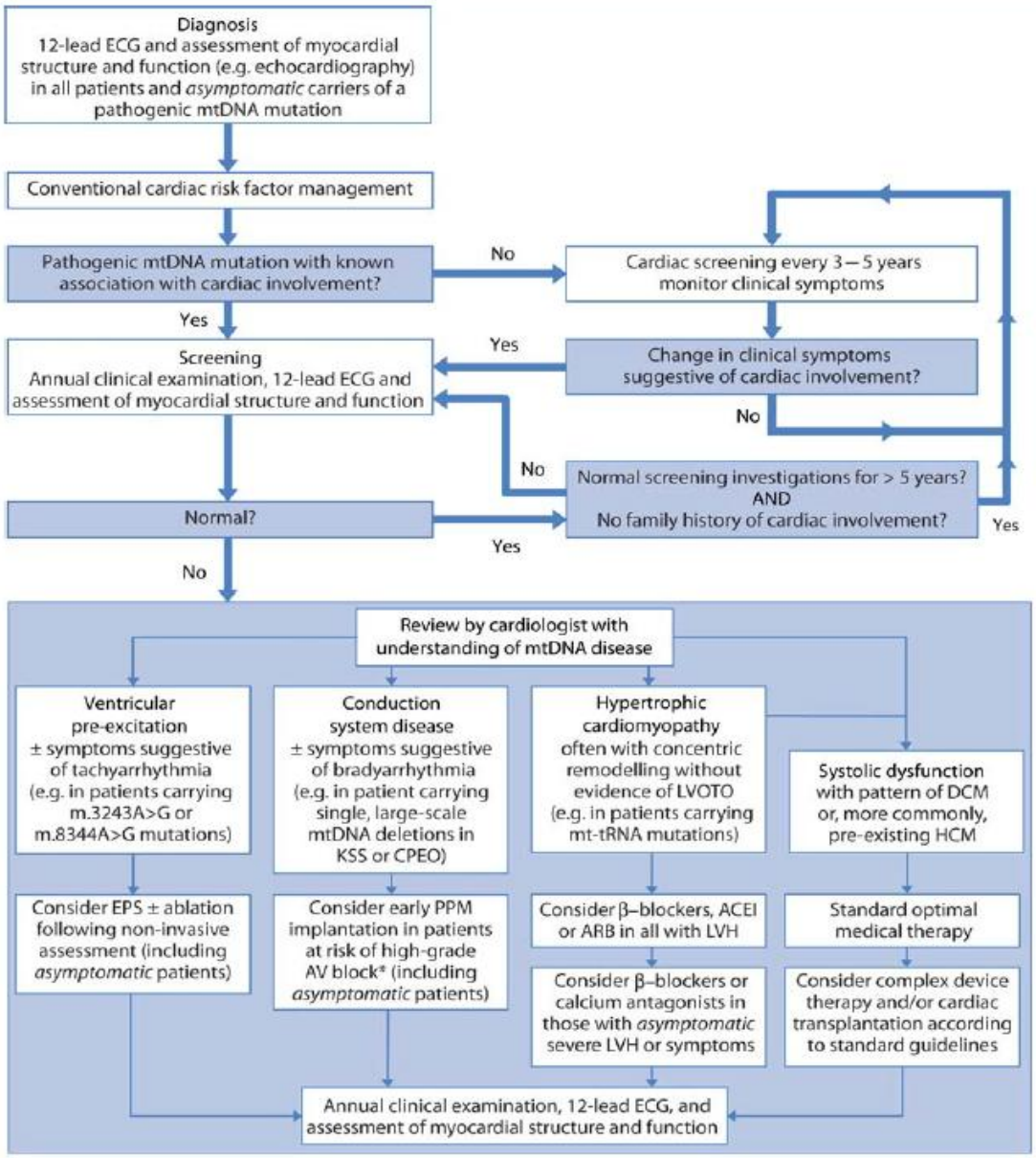


MELAS CMP : M/15yr



Cardiac Management

- First appreciation of LVH :
  - Beta-blocker
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptor blockers
- Heart Failure :
  - Angiotensin converting enzyme inhibitors
- Complex device therapy : ICD, CRT
- Cardiac transplantation : *controversy*



Bates MG et al. Eur **Heart** J. (2012) ;33:3023-33

Ongoing Study - Subjects

Table 1. Baseline characteristics of subjects			
	MD(N=34)	Control(N=34)	p-value
Sex(M:F)	22 : 12	14 : 20	
Age(year)	10.3 ± 4.0	8.4 ± 3.9	0.07
Weight(kg)	30.0 ± 12.7	30.0 ± 16.6	0.53

Eun L et al. in press 2015

Ongoing Study - Results

Table 2. Comparison of Echocardiographic measurement			
	MD(N=34)	Control(N=34)	p-value
LV EF (%)	65.94 ± 8.05	65.79 ± 4.02	0.99
LV FS (%)	36.31 ± 7.35	35.62 ± 3.06	0.62
IVSTd (mm)	7.75 ± 3.25	6.91 ± 1.56	0.19
IVSTs (mm)	9.97 ± 3.42	8.98 ± 1.81	0.15
LVIDd (mm)	36.06 ± 6.92	37.83 ± 5.86	0.28
LVIDs (mm)	23.15 ±5.8	24.34 ± 3.92	0.35
LV PWTd (mm)	6.06 ± 2.09	5.63 ± 1.57	0.36
LV PWTs (mm)	9.20 ± 2.88	8.68 ± 1.51	0.05
Mitral E (m/s)	0.98 ± 0.20	1.08 ± 0.16	0.03
Mitral A (m/s)	0.61 ± 0.20	0.54 ±0.11	0.08
Mitral E/A	1.77 ± 0.69	2.09 ± 0.45	0.04
TDI E' (m/s)	0.11 ± 0.03	0.14 ± 0.02	0.000
TDI A' (m/s)	0.08 ± 0.11	0.05 ± 0.02	0.23
TDI S' (m/s)	0.06 ± 0.01	0.09 ± 0.10	0.09
E/E'	8.88 ± 2.26	7.62 ± 1.64	0.01

Eun L et al. in press 2015

Conclusions

- Cardiac involvement in mitochondrial disease is common and an important predictor of morbidity and early mortality.

- Cardiologists will become more involved in the care of patients with mitochondrial disease as recognition of these disorders increases.

Thank You So Much !