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

- Proteinuria / Renal failure
- GL3 (globotriaosylceramide) deposition
- Angiokeratoma
- Cornea verticilata
- T1 Hyperintensity of pulvinar nuclei
- Hypohidrosis
- Acroparesthesia
- Hearing loss
- Tinnitus
- Early stork/TIA
- GI dysmotility
Strain Rate of Fabry’s dz

“Double Peak” sign of basal lateral wall
CMR with LGE in Fabry

Ischemic
A. Subendocardial Infarct
- DCM
- Myocarditis

B. Transmural Infarct
- RV Pressure Overload
- Sarcoidosis
- Myocarditis
- Anderson-Fabry's disease
- Chagas' disease

Nonischemic
A. Midwall HE
- RV Pressure Overload
- Sarcoidosis
- Myocarditis
- Anderson-Fabry's disease

B. Epicardial HE
- Sarcoidosis, Myocarditis, disease, Chagas' disease
- Global Endocardial HE
C. Global Endocardial HE
- Amyloidosis, Systemic Sclerosis, Post cardiac transplantation

"Double Peak" sign of basal lateral wall
Etiology of Hypertrophic Cardiomyopathy

- **Sarcomeric protein gene mutation**: 40-60%
- **Unknown**: 25-30%
- **5-10%**

Other genetic and non-genetic causes:

- **Inborn errors of metabolism**
  - Glycogen storage diseases:
    - Pompe
    - Danon
- **AMP Kinase (PRKAG2)**
- **Carnitine disorders**
- **Lysosomal storage diseases**
  - Anderson-Fahry
- **Neuromuscular diseases**
  - Friedreich’s ataxia
  - FHL
- **Mitochondrial diseases**
  - MLLAG
  - MLRT
- **Malformation Syndromes**
  - Noonan
  - LEOPARD
  - Costello
  - ULC
- **Amyloidosis**
  - Familial ATTR
  - Wild type TTR (senile)
  - AL amyloidosis
- **Newborn of diabetic mother**
- **Drug-induced**
  - Tacrolimus
  - Hydroxychloroquine
  - Steroids
Syndromic HCM

Noonan syndrome
- Webbed neck

LEOPARD
- Lentigines

Costello syndrome
- Large mouth, thick lips
- Excessive skin dorsum
- Deep palmar crease

Friedreich’s ataxia
- Hammer toes

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Genetic cardiomyopathies
HFCT 2017
<table>
<thead>
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<th>Therapeutic options</th>
<th>Treatment Options</th>
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<tr>
<td>Anderson-Fabry disease</td>
<td>Recombinant human α-galactosidase A</td>
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<td>Friedreich ataxia</td>
<td>Idebenone</td>
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<td>Transthyretin amyloidosis</td>
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<td>Pompe disease</td>
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<td>Tacrolimus-induced HCM</td>
<td>dose reduction/discontinuation</td>
</tr>
<tr>
<td>Danon disease</td>
<td>Heart transplantation</td>
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</tbody>
</table>
Genetic Testing

Prognosis

To identify

HCM (w/o LVH)

"Genotype + Phenotype -"

Follow-up

HCM (w/ LVH)
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

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

Mitochondrial cytopathies

Intercalated disc protein mutation

Sarcoplasmic protein mutations

Familial, Unknown gene

Hemochromatosis

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European Heart Journal 2008;29:270-276
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 18% of sporadic cases. Incorporation of sequencing approaches that detect TTN truncating mutations into clinical genetic testing algorithms could identify a significant proportion of cardiomyopathy patients who may benefit from targeted risk-stratification and therapeutic strategies.
Genetic Contributors to DCM

- **TTN Truncations**
  - ~23% Familial
  - ~18% Sporadic
- No identified mutation
- Sarcomeric ~15%
- Lamin A/C ~5%

- MYH7
- TPM1
- TNNT2
- LMNA
- PLN
- LDB3
- ABCC9
- ACTN2
- CAPN3
- CTF1
- DES
- DGCR8
- TCAP
- VCL
### Associated Clinical Features Present in a Minority of Patients with DCM

<table>
<thead>
<tr>
<th>Associated Phenotype</th>
<th>Clinical Features</th>
<th>Comment</th>
<th>Associated Gene*</th>
</tr>
</thead>
</table>
| **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 |
| **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 |
Cardiolaminopathy - DCM caused by LMNA Mutations

Age associated Penetrance

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

- Age groups:
  - < 20 years: 1/15, 95% CI 2-40
  - 20-39: 31/47, 95% CI 51-79
  - 40-59: 66
  - > 60 years: 25/29, 95% CI 67-96, 3/3, 95% CI 30-100

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 $\rightarrow$ cardiolipin remodeling

**Clinical:**
- Cardiomyopathy: DCM or LVNC
- Skeletal myopathy
- Growth retardation
- Neutropenia
- Increased urinary levels of 3-methylglutaconic acid
Arrhythmogenic Right Ventricular Cardiomyopathy
Arrhythmogenic Right Ventricular Cardiomyopathy

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

<1% (Naxos)

Desmin
C-terminus DSP
JUP
Rod DSP
PKP-2
N-terminus DSP

5-10% (Carvajal)

DSC-2
DSG-2

20-30%

5-10%

2-5%

Also:
TGFβ3
TMEM43
TTN

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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
Typical VT in ARVC
*LBBB/superior axis*

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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/m²)
  - PSAX RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥ 21 mm/m²)
  - or fractional area change ≤ 33%
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 $\geq 110 \text{ mL/m}^2$ (male) or $\geq 100 \text{ mL/m}^2$ (female)
  - or RV ejection fraction $\leq 40\%$

By RV angiography:
- Regional RV akinesia, dyskinesia, or aneurysm
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
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
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
Prognostic Stratification of Patients with ARVC

**Major Arrhythmic Events**
- Cardiac arrest due to ventricular fibrillation
- Sustained ventricular tachycardia

**High Risk**
- >10%/yr

**Major Risk Factors**
- Unexplained syncope
- Nonsustained ventricular tachycardia
- Severe right or left ventricular dysfunction

**Intermediate Risk**
- 1–10%/yr

**Minor Risk Factors**
- Proband status, male sex
- Frequent PVBs (≥1000/24 hr)
- Inducibility on electrophysiological study
- Extent of negative T waves
- Amount of right ventricular fibrofatty scarring
- Multiple desmosomal gene mutations

**Low Risk**
- <1%/yr

**No Events or Risk Factors**
- Healthy gene carriers
- Patients with definite ARVC
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

Genetic cardiomyopathies
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