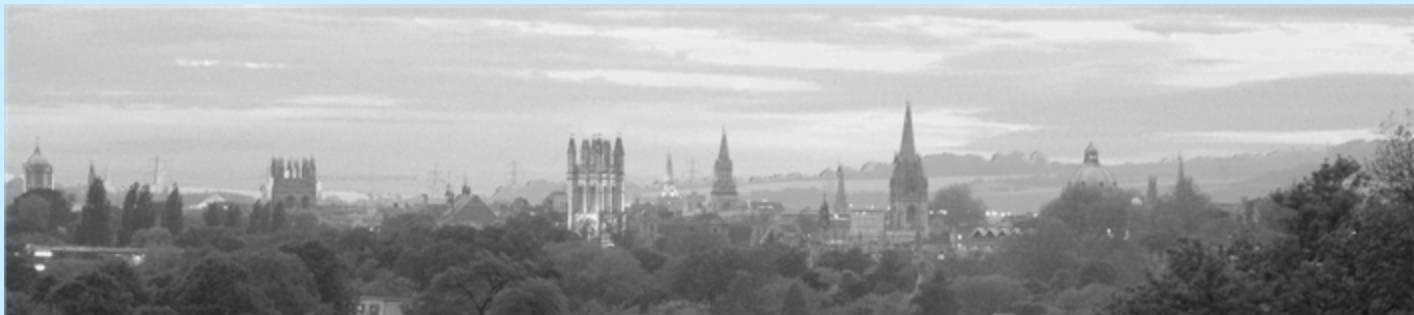


# How to manage a family with two cases of “Dilated Cardiomyopathy” OR...

Dr Edward Blair  
Oxford



Lets give the geneticist the ....



# Idiopathic Dilated Cardiomyopathy (DCM)

- Unexplained

LV dilatation & depressed contractility

- i.e. exclude obvious known causes:  
CAD, hypertension etc



- Pathology: myocyte hypertrophy, myocyte loss, fibrous replacement

- <1/2000



# How often is idiopathic DCM an inherited disease?

- *Familial recurrence*
- Until late 1980s: 1-2%
- Michels 1992; Keeling 1995; Baig 1998 etc:
- 25% DCM is familial by conservative criteria
- more if:
  - large families
  - include LVE
  - prospective follow up

In reality: probably 50% familial

Why was this not obvious?

Partial penetrance

Variable expression

Not looked for -

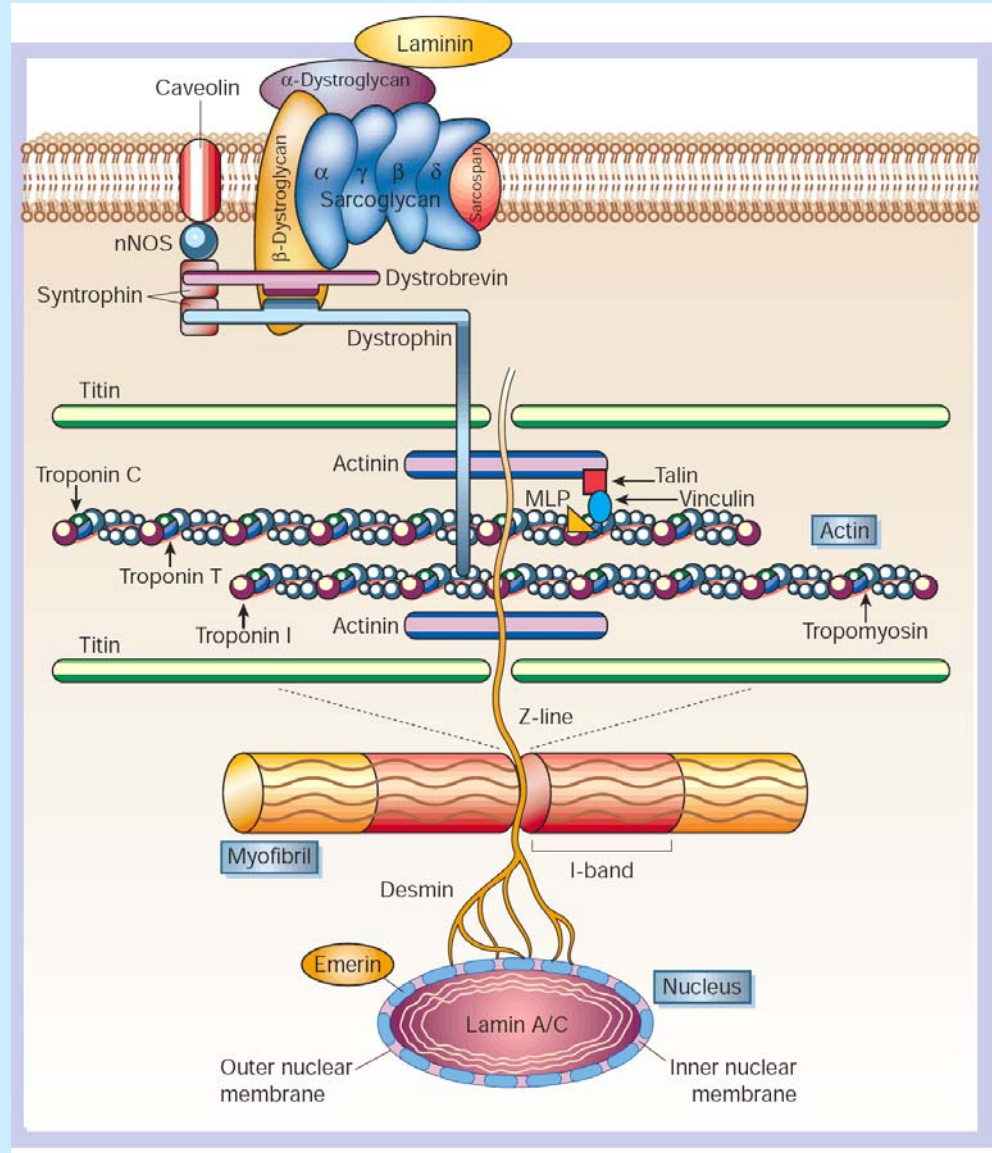
heart failure attributed to CAD etc...

CYTOSKELETON

dystrophin  
desmin  
 $\delta$ -sarcoglycan  
actin

Z DISC

Titin  
Metavinculin  
ZASP



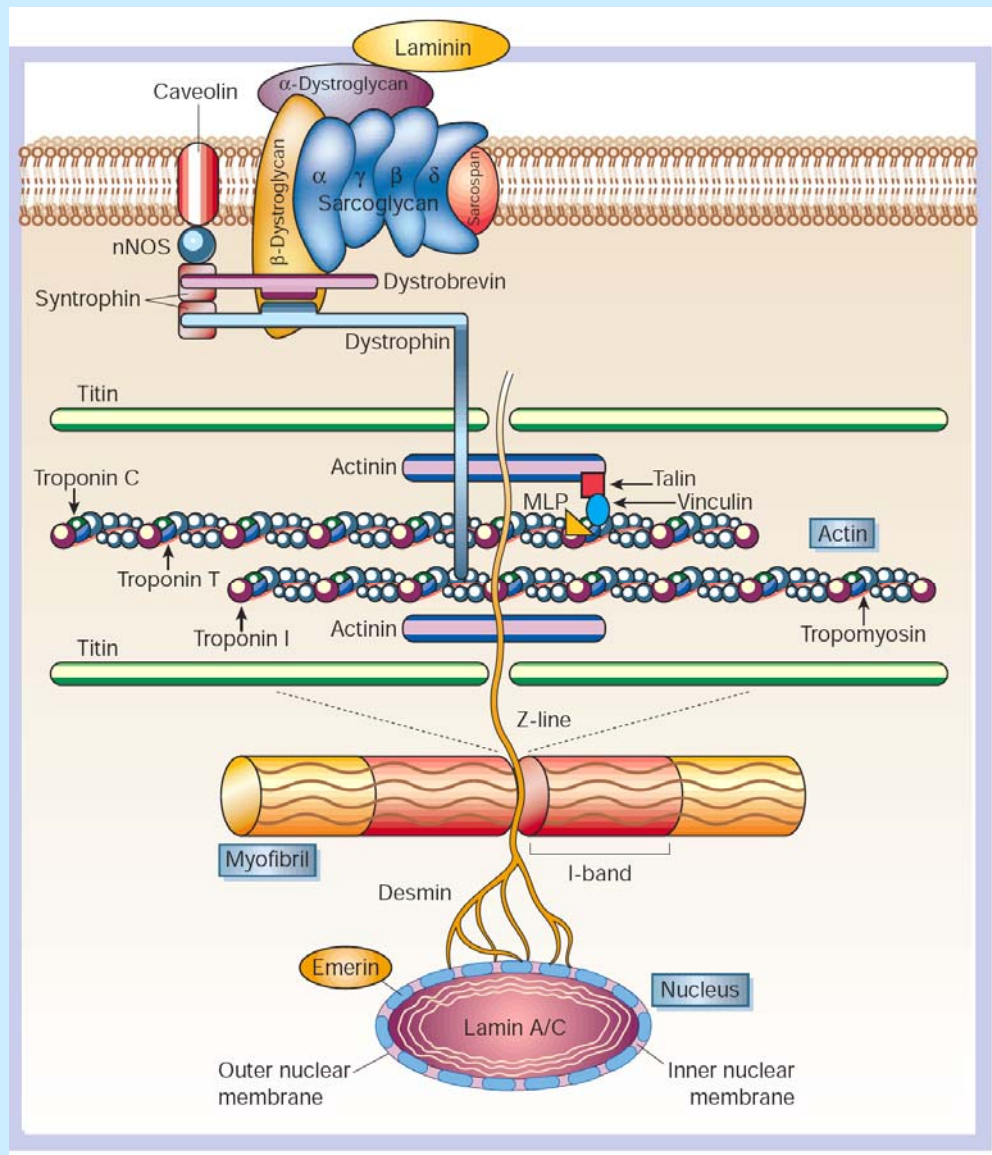
SARCOMERE

$\beta$ -myosin  
troponin T  
 $\alpha$ -tropomyosin  
troponin C  
troponin I

NUCLEAR ENVELOPE

lamin A/C  
emerin

SIGNALLING: phospholamban, SUR2a



Interpret Candidate Gene studies with caution!

# How to manage a family with two cases of “Dilated Cardiomyopathy”

- Pedigree assessment
- Associated features
- Investigations
  
- Pragmatism

Two cases = Genetic?

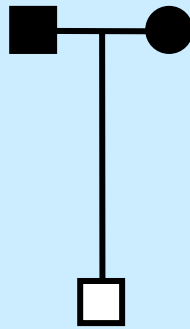
# Two cases = Genetic?

## Pedigree assessment

- Mendelian
- Gene vs. non gene explanation
- Defined ICC - HCM, ARVC, LVNC?

# Mendelian or Not?

- Husband and wife or father and son



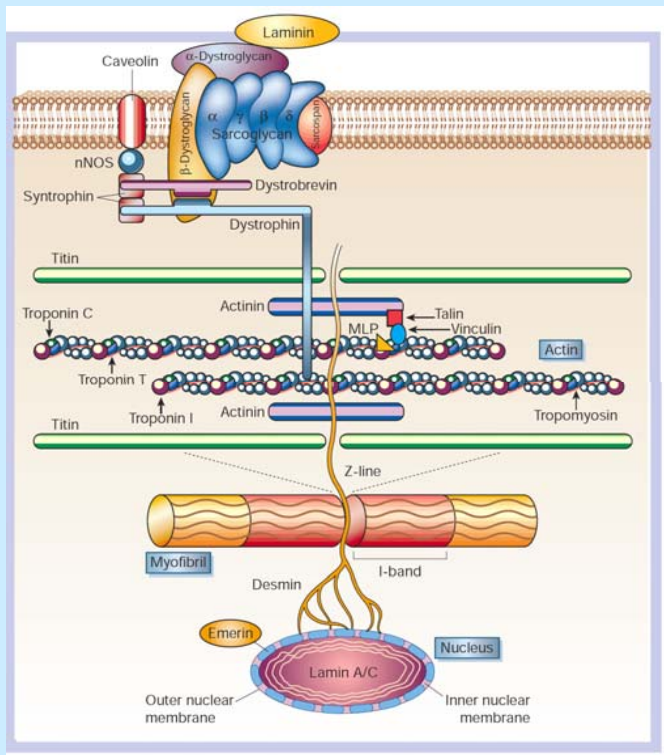
Environmental factors?  
Multifactorial, common?  
Met at HRC 2009?



Genetic unless other  
obvious explanation?

# Autosomal dominant

- 80-90% of adult cases?



## SARCOMERE

β-myosin

troponin T

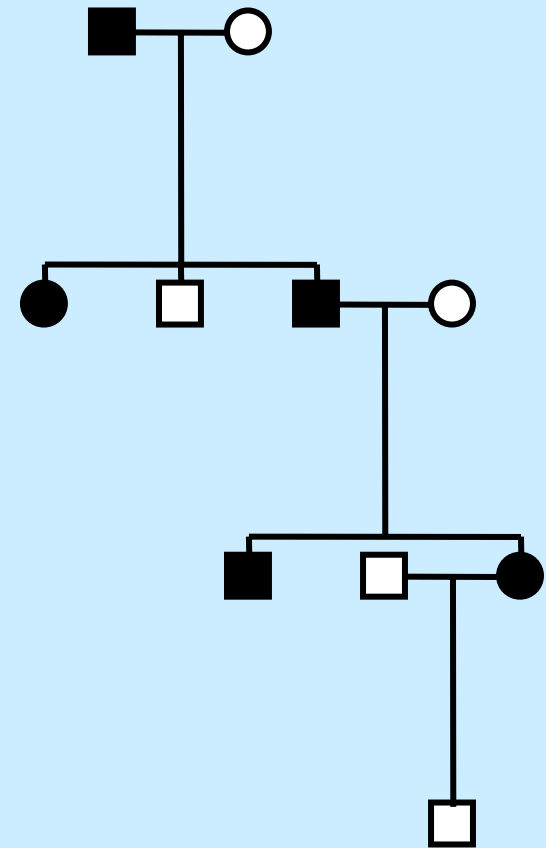
α-tropomyosin

troponin C

## NUCLEAR

## ENVELOPE

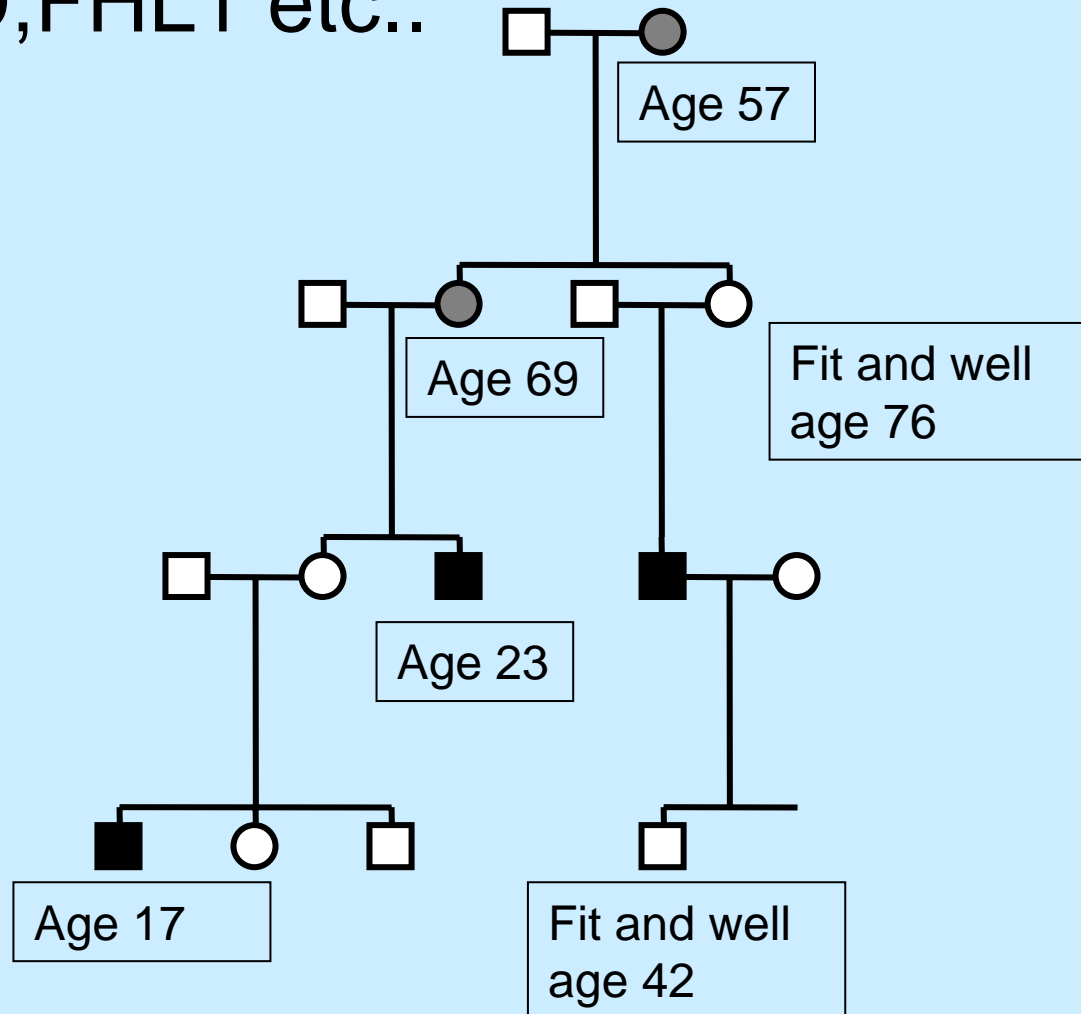
lamin A/C



SIGNALLING: phospholamban,

# X-linked recessive

- BMD/DMD, FHL1 etc..



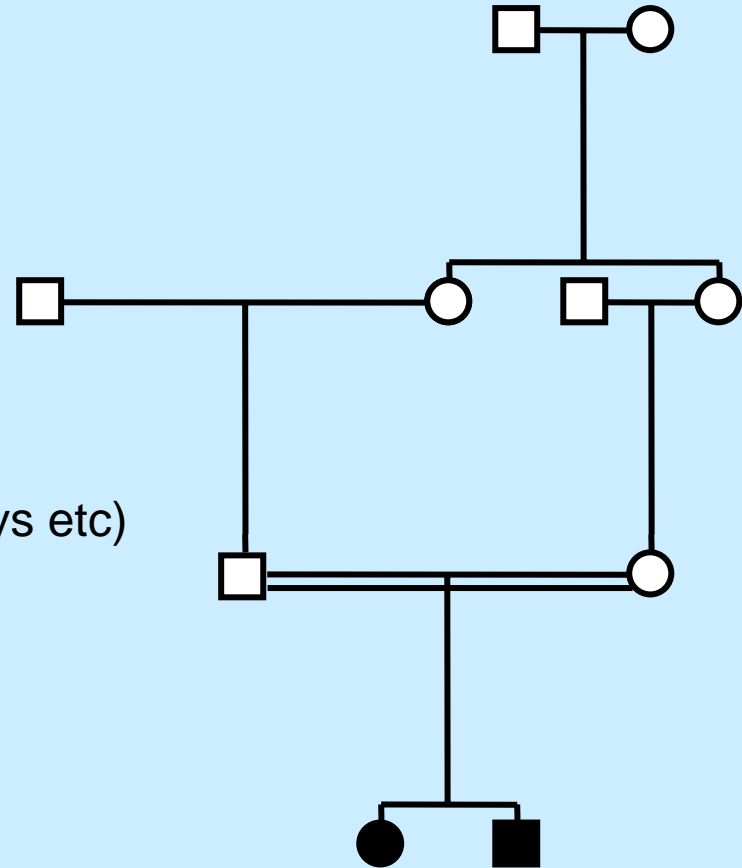
# Autosomal Recessive

Consanguinity makes this more likely  
In UK consanguinity often not present

Metabolic

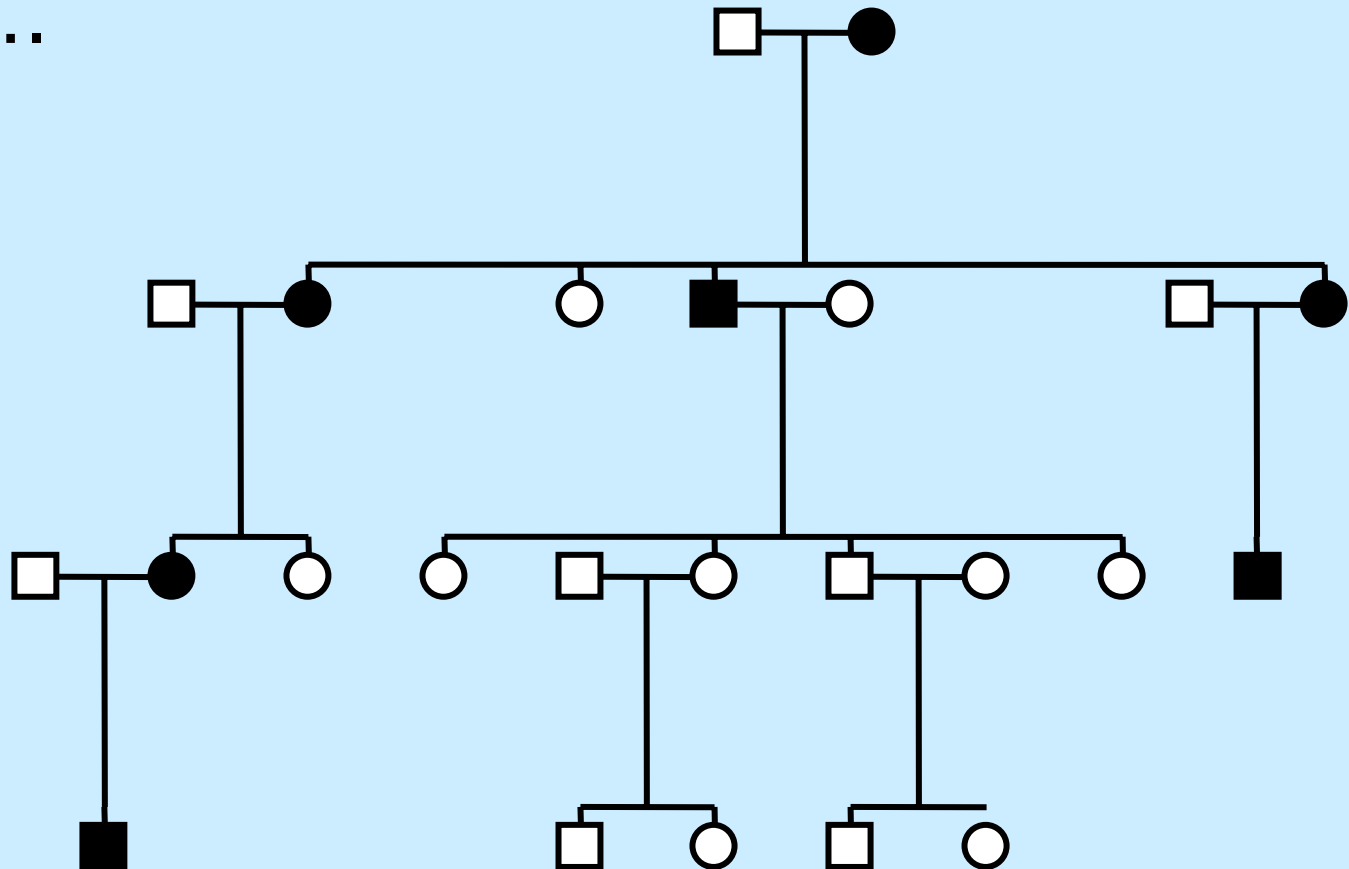
Young onset

Other systems involved (brain, liver, kidneys etc)



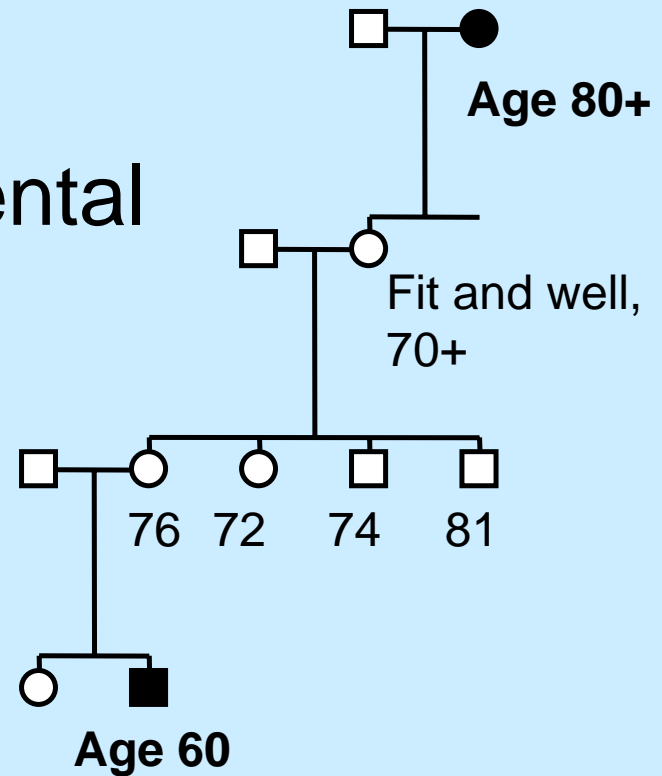
# Mitochondrial inheritance

- Diabetes, “metabolic features”, retinopathy etc....

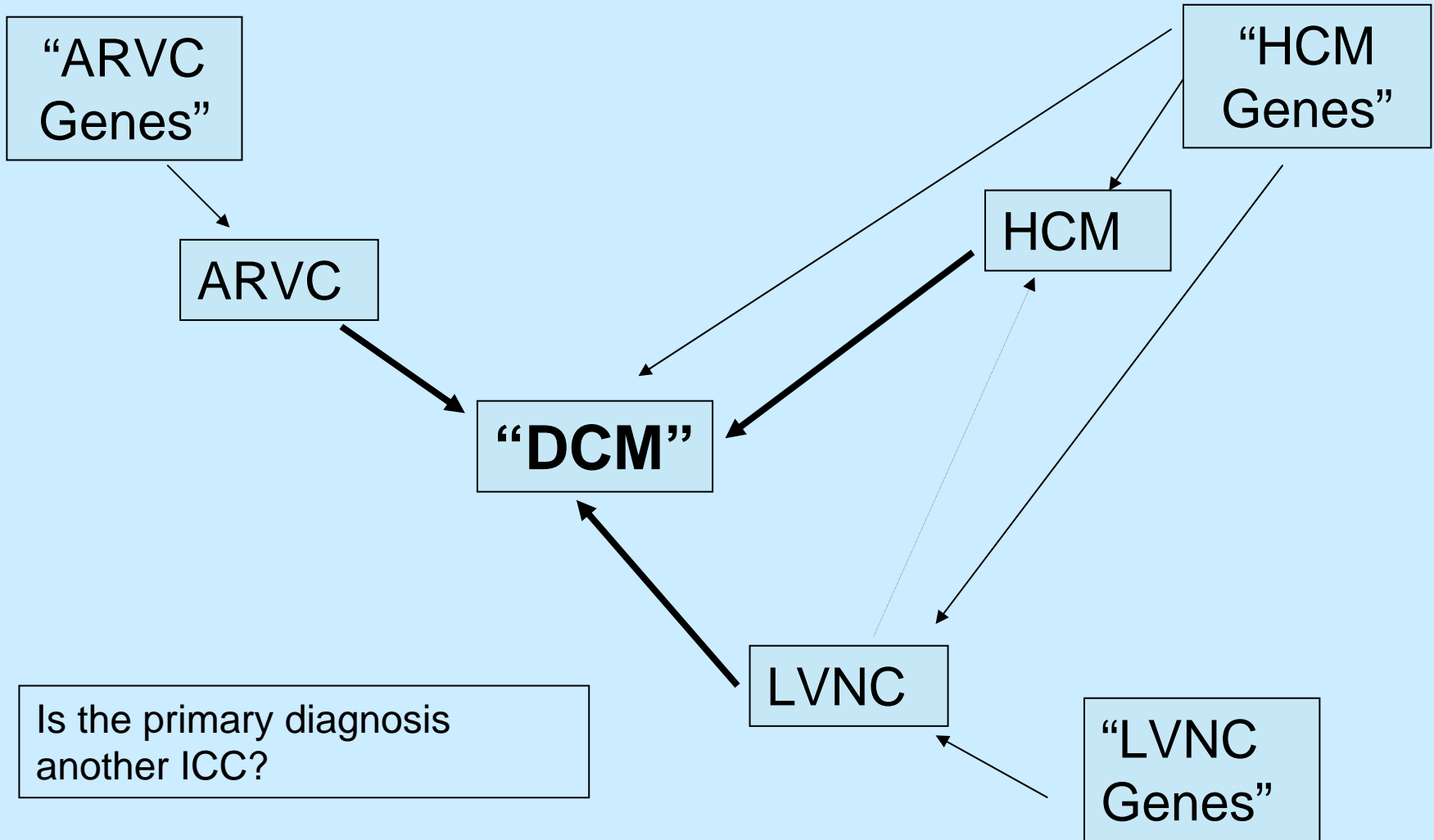


# Genetic?

- Non penetrance, variable expression etc...
- Gene vs. No gene
- Multifactorial, environmental



# “DCM” mimicked by other ICC



# Associated Clinical Features

Clues to mode of Inheritance and  
Syndromic diagnoses

# Associated Clinical features

## 1) DCM with skeletal muscle involvement

overlap syndromes:

Dystrophin	DCM <-> Duchenne/Becker
------------	-------------------------

$\delta$ -sarcoglycan	DCM <-> limb girdle muscular dystrophy
-----------------------	--

Lamin A/C	DCM <-> limb girdle muscular dystrophy
-----------	--

Desmin	DCM <-> desmin myopathy
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$\beta$ -MHC	DCM <-> distal myopathy
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Mitochondrial	DCM <-> mitochondrial myopathy
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Think of it! Measure CK

Molecular genetics available - dystrophin, lamin, LGMD, mt

## 2) DCM with conduction disease

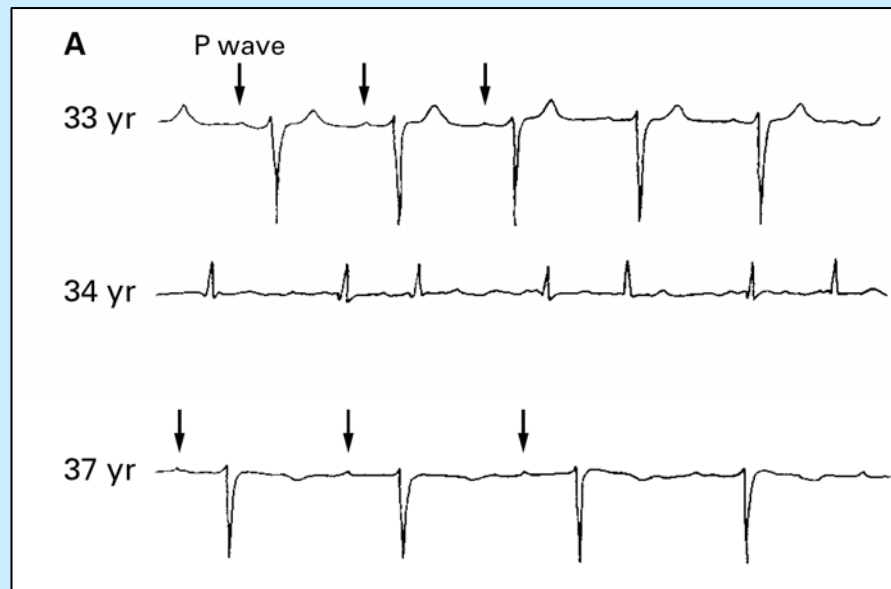
Lamin A/C

sinus & AV node disease; may precede DCM

check CK

SCN5A

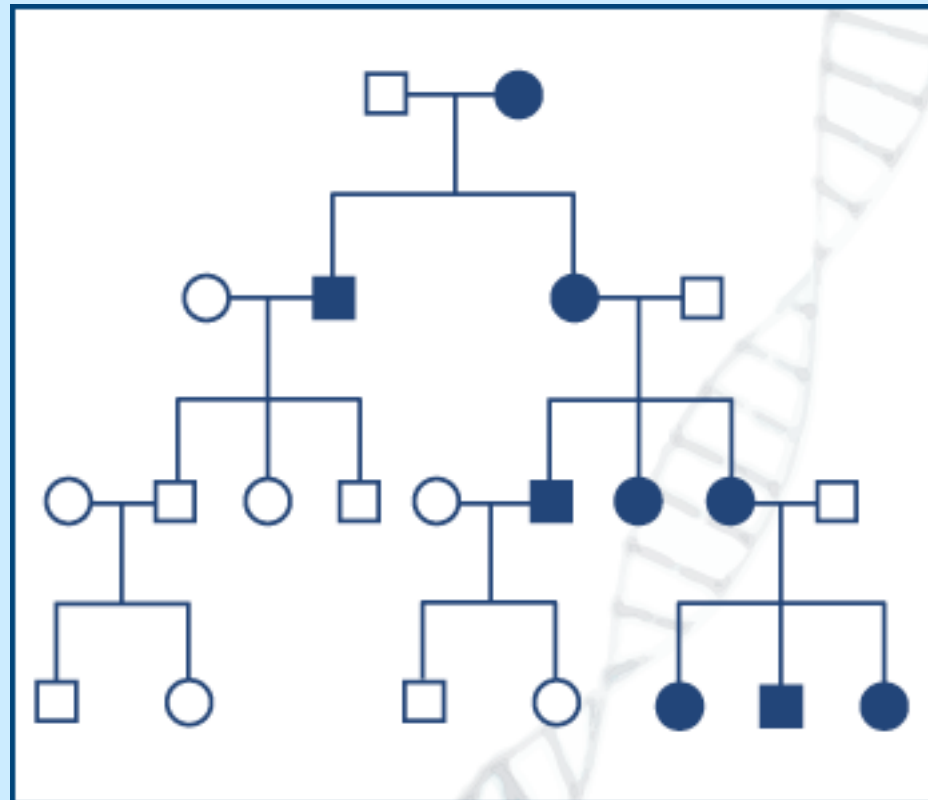
other loci - genes unknown



### 3) DCM with deafness

Autosomal dominant; one locus - EYA4 implicated

Mitochondrial - e.g. tRNA mutations

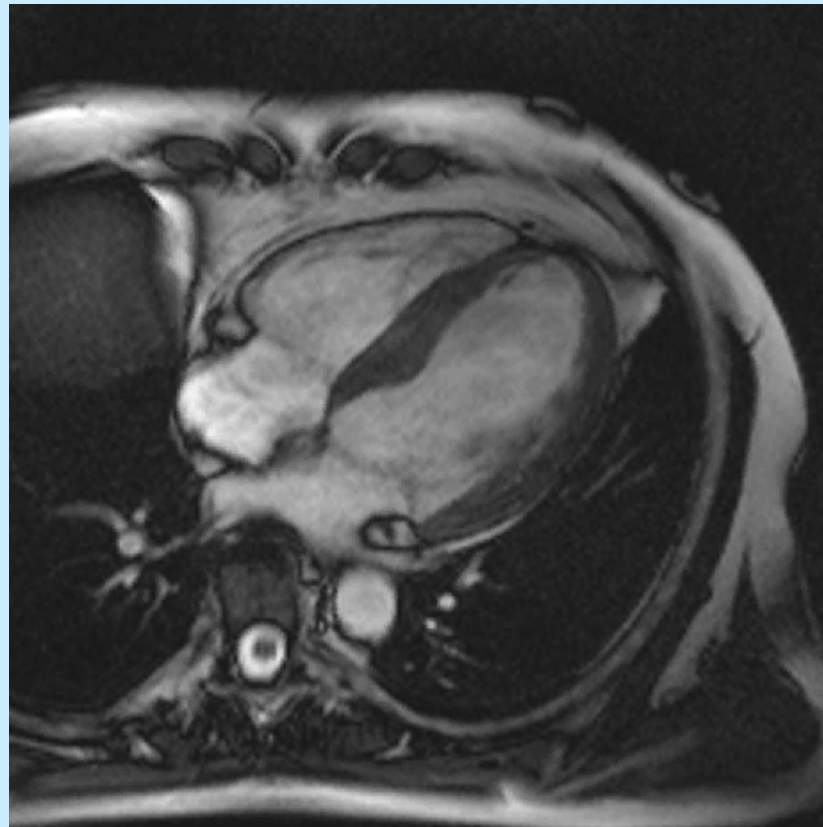


#### 4) DCM with hypertrophy

'burnt out' HCM

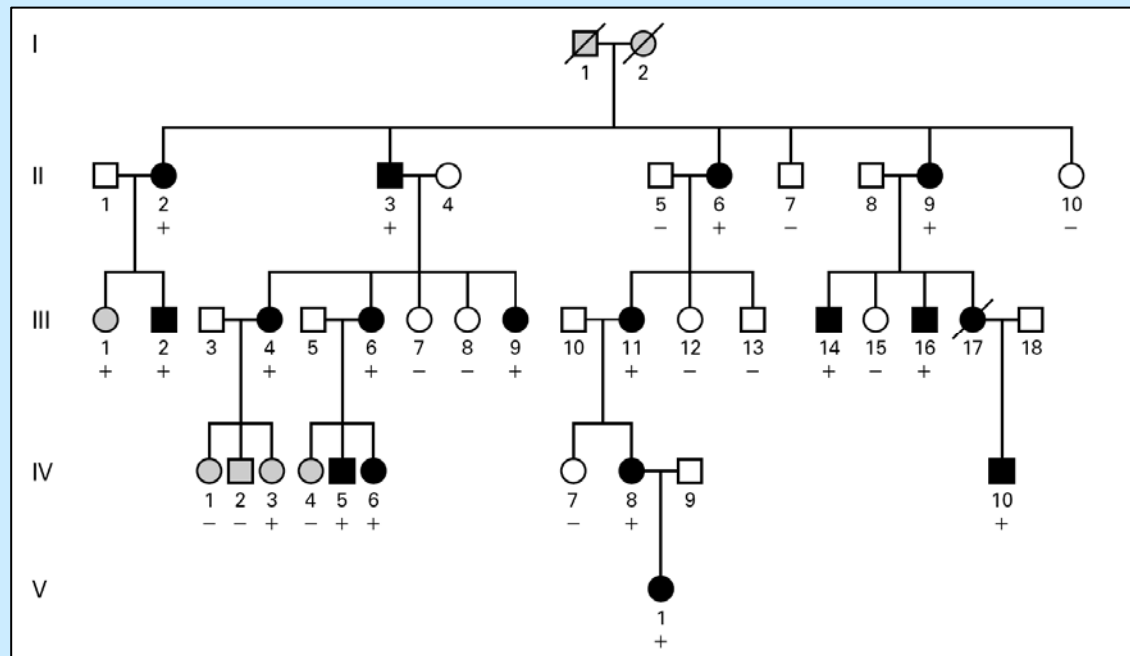
Metabolic myopathy - recessive enzyme defects, mito mutations

[Left ventricular non-compaction, LVNC]

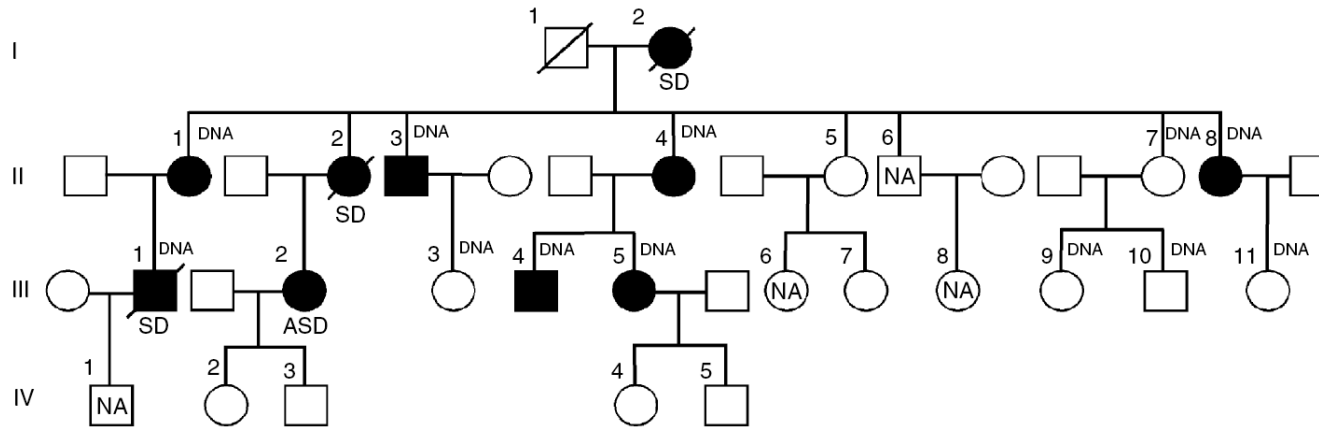


## 5) 'Pure' DCM - the commonest category

e.g. Sarcomeric DCM      'relatively common' - still ~5-10% of DCM  
early onset; ? bimodal



**Most familial DCM (e.g. 75%) still unaccounted for.....**



## Conduction disease, DCM

## & Brachydactyly

Clin Genet 2005; 68: 155–160.



LMNA mutation (c.1609-12T>G, IVS9-12 T>G)

# Investigation?

- Pedigree.

dominant history makes recessive metabolic disease less likely (80-90% of inherited DCM)

- Age of onset

early onset may suggest metabolic/  
mitochondrial/recessive disease

- Associated features

May provide diagnostic clues e.g. CK and blood biochemistry, ECG features, audiology etc

NB majority still “pure” autosomal dominant DCM

# Common Scenario

Dominant, X-linked, mitochondrial?

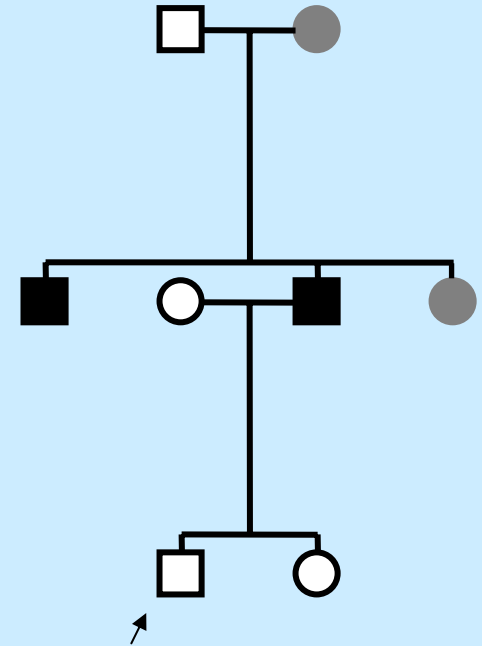
What are the actual lifetime risks?

What are his offspring risks?

Investigate? Modalities?

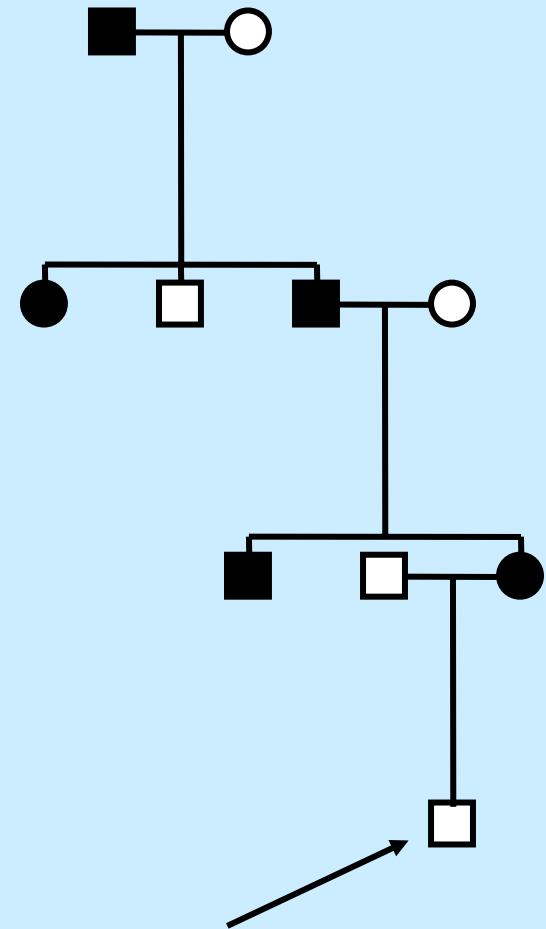
Continued surveillance? Frequency?

Genetic testing?



# Autosomal dominant

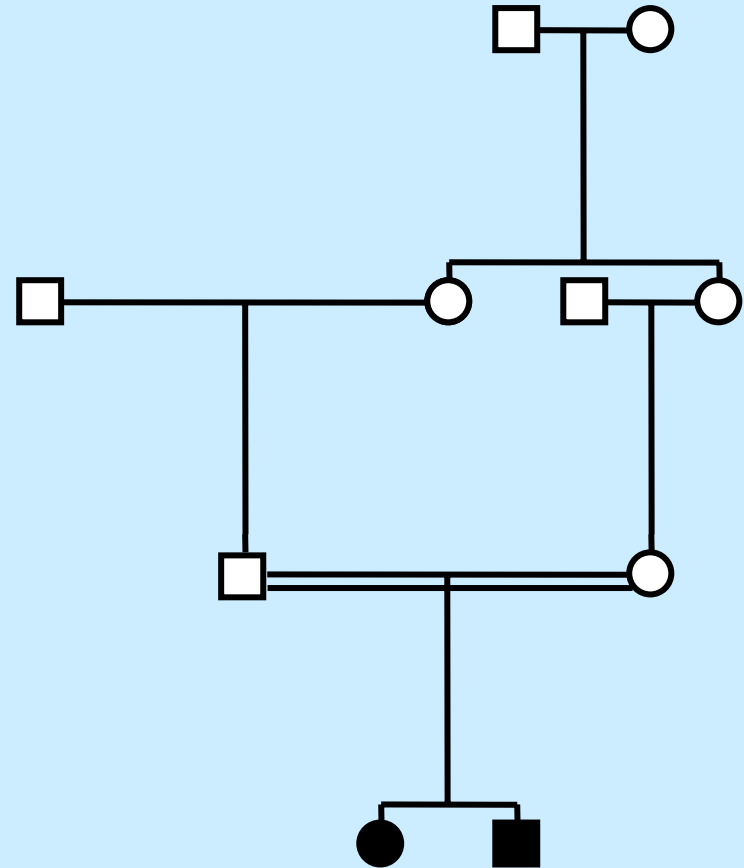
- Disease Risk =  $1/2 * \text{penetrance}$



# Autosomal Recessive

Disease Risk for next child  $\frac{1}{4}$

Penetrance likely to be close to 100%



# Can we work with single cases?

50% single gene

85% Autosomal dominant (AR, mito, XL of no concern)

AD gives 1 in 2 risk

Penetrance 80%?

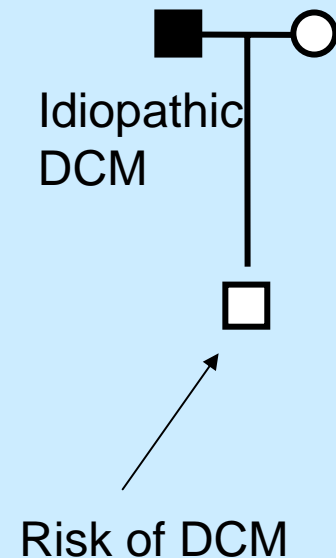
$0.5 * 0.85 * 0.5 * 0.8 = \text{about } 1/6$

Some level of reassurance?

Higher risk if mum affected

Maybe just a bit of fun because....

clinical follow up mandated?



## Implications for clinical practice

DCM-> idiopathic DCM -> offer screening to 1st degree relatives:

Family history - be inclusive. 3 generation

Clinical investigation - low threshold in families (e.g. LVE)

Look for associated: conduction disease

skeletal myopathy

metabolic/mitochondrial syndromes

overlap with other cardiomyopathies

If negative - ? repeat in 5 years

Consider DNA testing

# Conclusion

- DCM clinical and family management complex
- Guidelines pragmatic
- Genetics may guide management decisions (e.g. lamin and SCD risk)
- Molecular genetics still of some (limited) value for family cascade testing

