

The Big Debate





Association for Inherited Cardiac Conditions

Heart Rhythm UK Birmingham 2016



The Big Debate

This house believes that

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This house believes that

ALL Cardiologists should be ordering ALL Genetic tests

Motion is correct

Implement as soon as feasibly possible

Debate has a bad reputation.....



Ground Rules



Ground Rules

Dr Graham Stuart

When a woman says
“**Just do what you want.**”

Do NOT under any
circumstances
do what you
want.

*Unhinged maverick
Sees the future more clearly.....*

Dr Saru Mehta



*Rational and plausible
The safe choice.....*

This house believes that

ALL Cardiologists should be ordering ALL Genetic tests

- History of genetics and cardiology
- Phenotype versus Genotype
- Mainstreaming of genetic testing
- The future.....

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Genetics and Cardiology

- a personal history



Master Graham Stuart

Schoolboy 1976

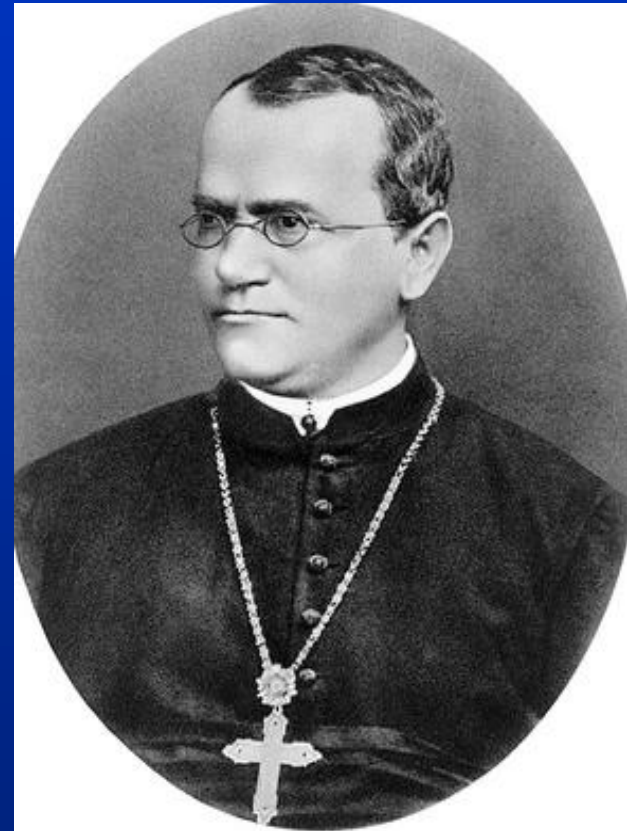


Genetics and Cardiology

- a personal history



Dr Graham Stuart MBChB
1982



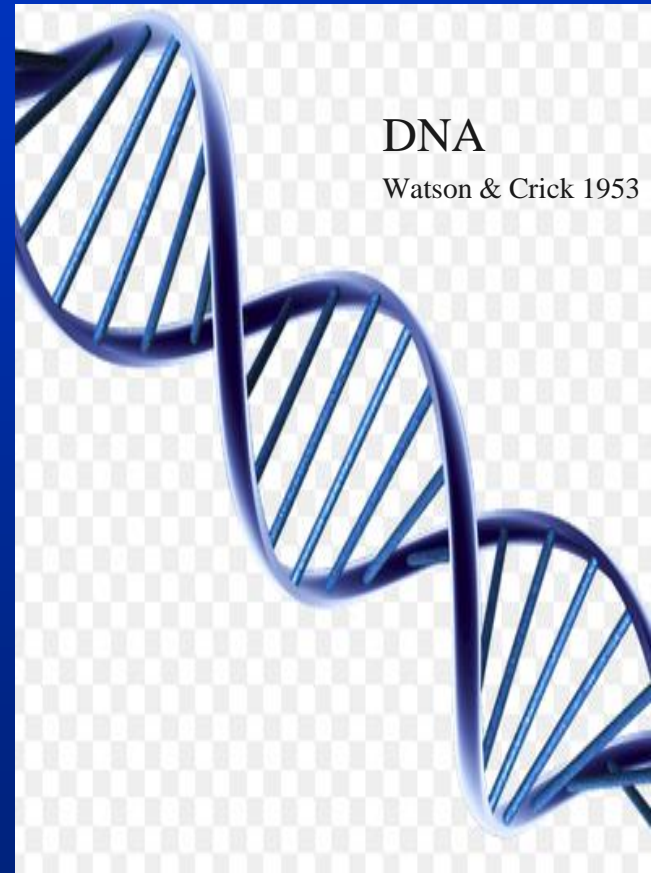
Gregor Mendel
1822- 1884

Genetics and Cardiology

- a personal history



Dr Graham Stuart MBChB
1982



Genetics and Cardiology

- *a personal history*



Dr Graham Stuart MBChB MRCP
1985 -1992

DiGeorge syndrome with isolated aortic coarctation and isolated ventricular septal defect in three sibs with a 22q11 deletion of maternal origin
Wilson et al Br Heart J 1991;66:308-312



Coarctation of aorta

Genetics and Cardiology

- a personal history



Dr Graham Stuart MBChB FRCP FRCPCH
1993



Sally Davies

"Prof Harper wants me to set up a Marfan clinic"

MARFAN SYNDROME

aetiology: abnormal fibrillin

1986 Fibrillin discovered

Sakai et al J Cell Biol 103:2499-2509



MARFAN SYNDROME

aetiology: abnormal fibrillin

1986 Fibrillin discovered

1990 Abnormal fibrillin noted in
Marfan syndrome

Hollister New Eng J Med 1990;323:148-153

MFS linked to chrom 15

Kainulainen New Eng J Med 1990;323:935-939

MARFAN SYNDROME

aetiology: abnormal fibrillin

1986 Fibrillin discovered

1990 Abnormal fibrillin noted
in MFS

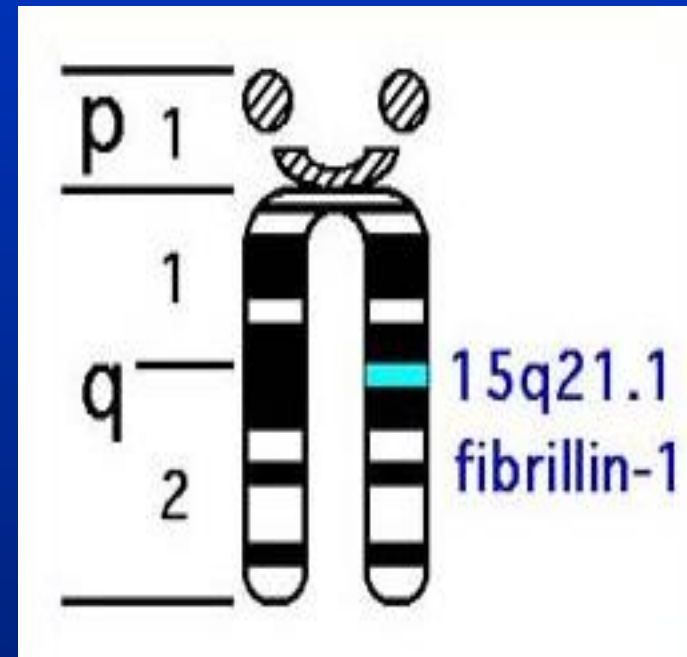
MFS linked to chrom 15

1991 Fibrillin - 1 gene linked
to Chrom 15

Lee et al Nature 1991;352:330-334

Dietz Nature 1991; 352:337-339

> 600 mutations found



MARFAN SYNDROME

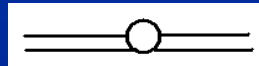
aetiology: ? dominant negative effect

Chrom 15 deletion

50% cells



Abnormal fibrillin



Abnormal myofibrils



Abnormal elastin



But....



A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*

Loeys et al Nature Genetics 2005;37(3):275-281

nature
genetics

- Some “Marfan” patients had tortuous vessels



All “mutations are not detected by **all** genetic tests

variations

del/dups/copy number

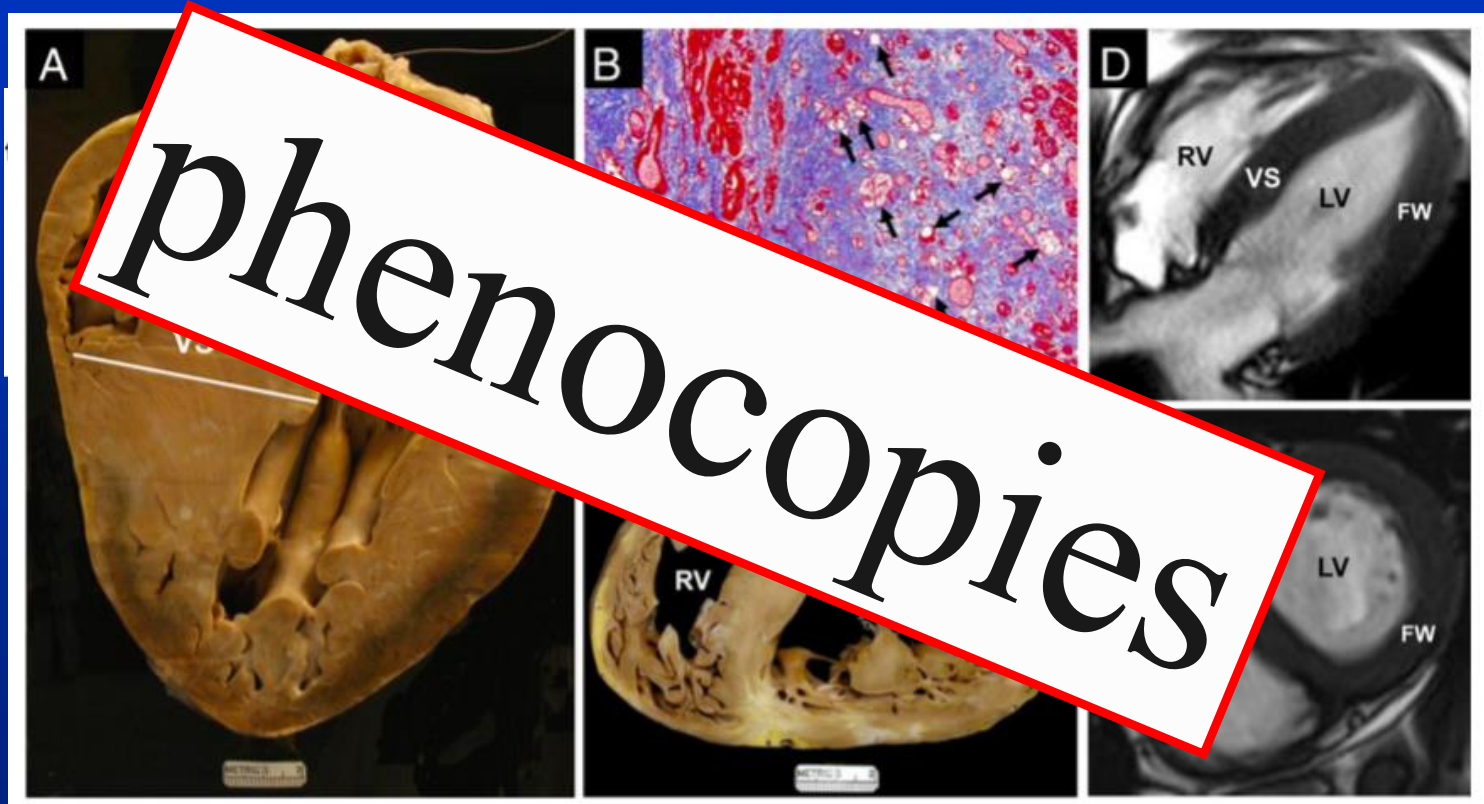
- Some “Marfan” patents had tortuous vessels
- Some Marfan patients had negative testing



Genetics of Hypertrophic Cardiomyopathy After 20 Years

Barry J. Maron, MD,* Martin S. Maron, MD,† Christopher Semsarian, MB, BS, PhD‡

JACC Vol. 60, No. 8, 2012
August 21, 2012:705-15



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Table 3 Current Criteria Used to Determine Probability for Pathogenicity of an HCM Mutation*

Pathogenicity Criterion	Description	Potential Limitations for Interpretation
Cosegregation	Determine whether mutation is present in relatives with LVH and absent in those without LVH	Often impractical Family size may be small/relatives unavailable Family compliance unpredictable Requires resources for imaging/DNA studies in ≥ 3 relatives (other than proband) including ≥ 1 with HCM phenotype†
Prior evidence of pathogenicity	Documentation that mutation is HCM disease-causing in ≥ 1 patient in published literature, or in the individual experience of a testing laboratory	Absence of established comprehensive, curated, and cooperative database tabulating mutations‡ High rate of novel (de novo; "private") mutations in 65% of probands Interpretation of pathogenicity can be inconsistent among testing laboratories
Control population	Confidence for pathogenicity increased when mutation absent from large, ethnicity-matched ostensibly healthy population	Often insufficient size§ Control subjects should be unrelated, ethnicity-specific and free of the disease in question Potentially pathogenic variants can occur in subjects judged clinically normal Many rare benign (missense) variants in normals, termed "background noise"
Major disruption protein structure, and function	Mutant proteins are judged to have substantially altered physical properties	Inferred from evidence obtained from in nonhuman sources¶

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phenocopies

Variants of unknown
significance

How do we deal with phenocopies and variants of unknown significance ?



Detailed and informed
Cardiac assessment !

Language Problem



Geneticists and
cardiologists speak different
languages !

Genetics and Cardiology

- a personal history



Marfan clinic = aortopathy clinic

Congenital clinic = ICC clinic
cardiomyopathy
sudden death clinic
inherited arrhythmia clinic

Dr Graham Stuart MBChB FRCP FRCPC
Move to Bristol 1998

Genetics and Cardiology

- a personal history



2012 ICC clinic weekly

2013 ICC MDT monthly

2016 West of England

Genomic Medical Centre

Dr Graham Stuart MBChB MSc FRCP FRCPCH

1998 -2008

Cardiology Journals and Genetics

Mimics of Hypertrophic

Genotyp
assessment

Whole Exome Molecular Autopsy Following Exertion-Related Sudden

Unexplained Death in the Young

rization
milies

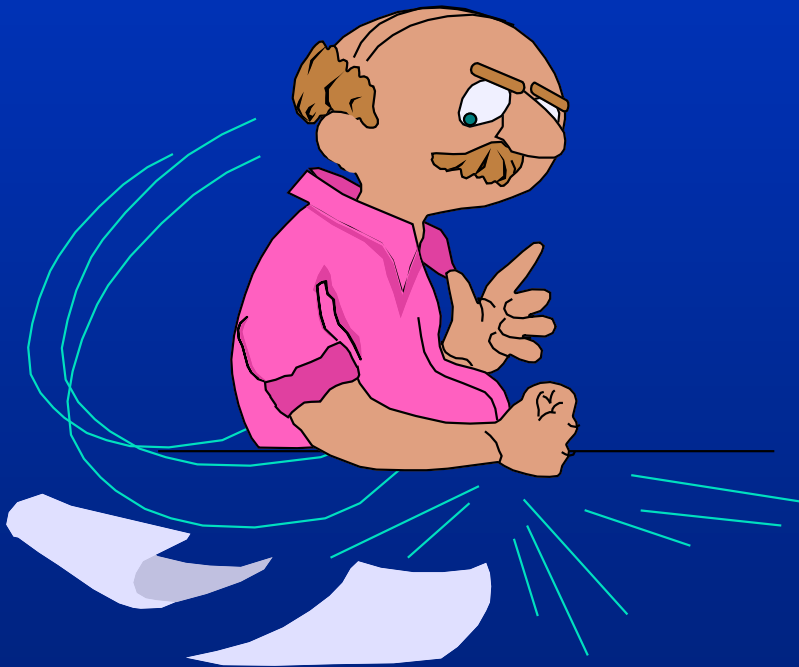
targeting in Myo
for Cardiac

ckerman, M
congen

A Modern Approach to Classify Missense
Mutations in Cardiac Channelopathy Genes

ndrome

**Can a cardiologist read a cardiology
journal without understanding genetic
testing?**



No !

This house believes that

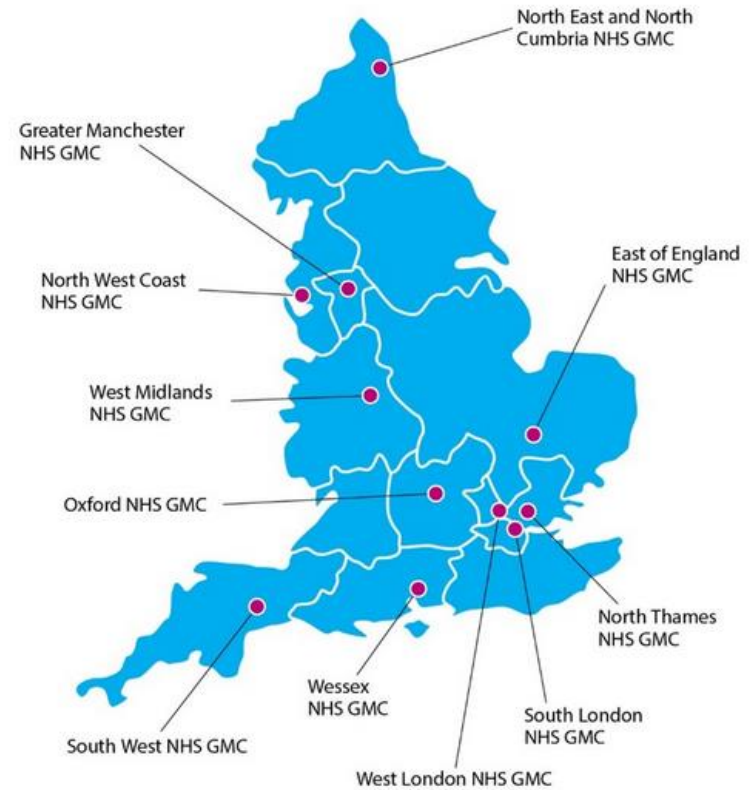
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Mainstreaming and the Future



About Us ▾ | 100,000 Genomes Project ▾

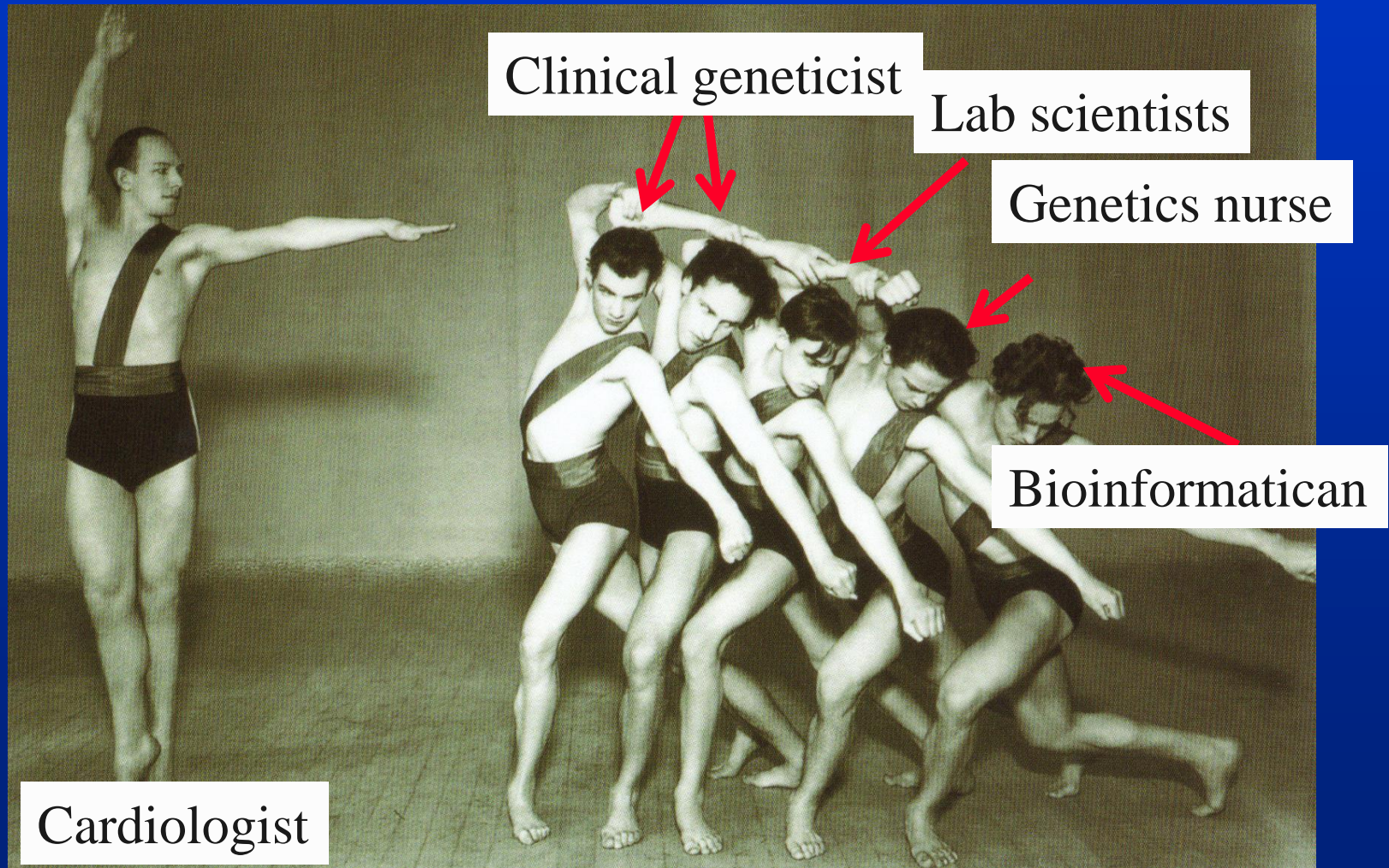


● Lead organisation

Cardiologists need to order their own genetic tests...



The Cardiac Genetics Team



Thank you

Rebuttal

Phenotype vs genotype



“In the post-genomics era, phenotype is king. We have excellent tools for mappings genomes but there is a bottleneck when it comes to phenotypes....the answer is understanding the interaction between environment and traits”

Dr Jose Jimenez- Berni

National Science Agency, Australia

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