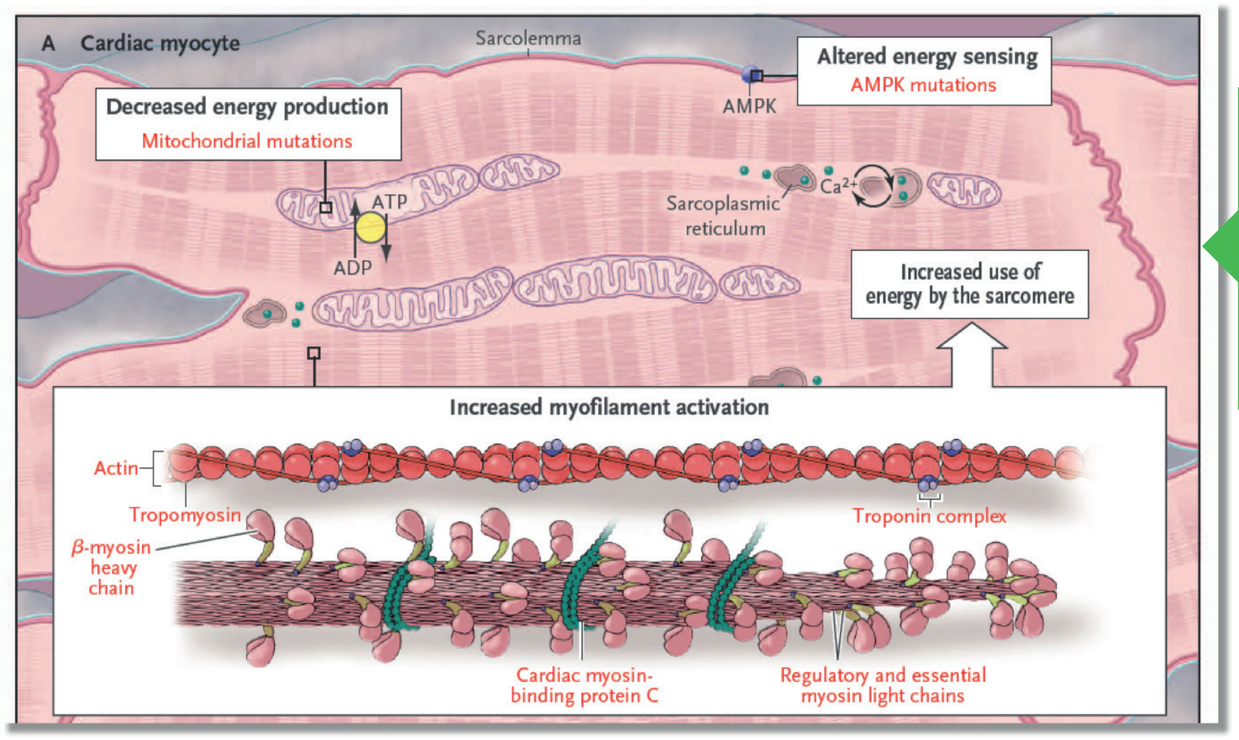
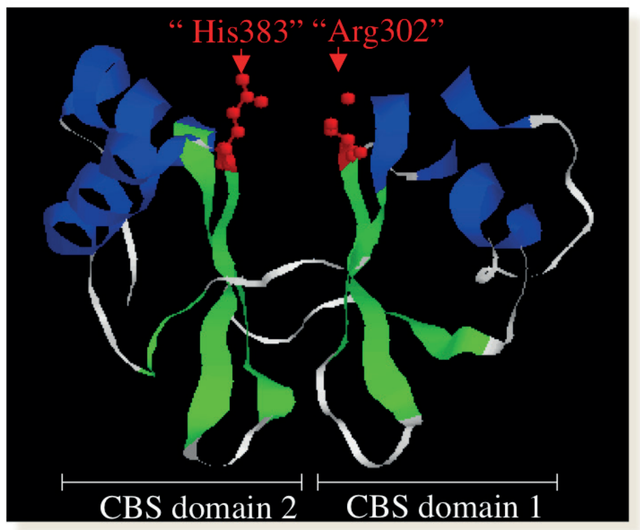
The Wellcome Trust Centre for
Human Genetics

UNIVERSITY OF OXFORD

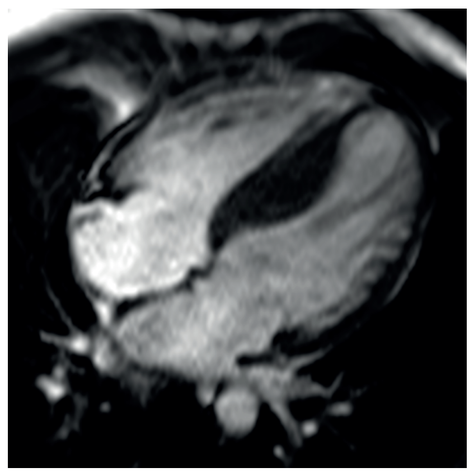
A rare inherited cardiomyopathy points the way to understanding disease mechanisms



Where the contraction of heart muscle either wastes too much ATP (myofilament mutations), cannot sense normal ATP homeostasis (AMPK mutations) or cannot produce enough energy to meet demands (mitochondrial mutations), the heart develops hypertrophy and the risk of life threatening cardiac rhythm abnormalities



Missense mutations in the gamma 2 isoform of AMPK are situated precisely in the nucleotide binding cleft, preventing the normal tonic inhibition by ATP and the activation by AMP that follows cellular stress



A cardiac magnetic resonance image of a heart affected by hypertrophic cardiomyopathy showing marked increased thickness in the muscle that makes up the wall of the ventricle

WHAT WAS KNOWN

- The inherited heart muscle disease, hypertrophic cardiomyopathy (HCM), is the most common monogenic cardiac disease and the main cause of sudden cardiac death in young people
- Most families with the condition have mutations affecting the contractile proteins of the myofilament – the molecular motor of the heart muscle
- These mutations have diverse effects on fundamental muscle contraction making the final common pathway unclear

WHAT WE DID

- Identified a novel disease gene in two families with a very rare variant of HCM in which affected individuals also show abnormal electrical conduction in the heart
- Found mutations in the nucleotide binding cleft of the gamma 2 isoform of AMPK, the 'fuel gauge of the cell'

WHAT THIS ADDS

- The finding in these very rare families suggested that failure to maintain the balance between energy supply and demand can cause HCM
- This fitted with experimental data showing that the diverse myofilament mutations all increase the energy cost of force production, leading us to propose energetic compromise as the final common pathway
- We have since confirmed energetic compromise in the hearts of patients and shown a new treatment to improve ATP supply in the heart to be successful in Phase II clinical trials
- We have shown that genetic testing for this and other HCM disease genes is a cost effective way of saving lives in families with HCM; with support from the Oxford Biomedical Research Centre we have taken genetic testing through to a commissioned national service in the NHS and international practice guidelines

REFERENCES

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