Magnet to Microscope, and Back:
CMR Prediction Rule for Preclinical Hypertrophic Cardiomyopathy

Authors: GCaptur,[1,2] TJ Mohun,[3] RWilson,[3] LR Lopes,[1,2] V Patel,[1,2] G Finocchiaro,[2] J Levine,[4] L Conner,[5] C Li,[6] P Bassett,[7] M Bennett,[3] DM Sado,[1,2] AS Herrey,[2] V Ferreira,[8] MT Esteban,[2] WJ McKenna,[1,2] V Muthurangu,[1,9] CE Seidman,[5] DA Bluemke,[10] CY Ho,[4] PM Elliott[1,2] & JC Moon[1,2]

Background: Familial hypertrophic cardiomyopathy (HCM) caused by sarcomeric protein mutations is the commonest identifiable cause of sudden death in the young so predicting genetic carriage in family members is important. Genotyping is not always fully informative. Structurally, sarcomere mutations appear to induce a preclinical HCM phenotype, consisting of cardiac changes before left ventricular hypertrophy (LVH) develops. We hypothesized that measuring these changes by cardiovascular magnetic resonance (CMR) would aid the prediction of mutation carriage identifying at risk individuals. We hypothesized that the structural changes of the preclinical HCM phenotype represented a persistence of embryonic cardiac traits into the adult form, so we sought to test this neotenization hypothesis in mice.

Methods: *Magnet:* Using a large, multi-site (12-centres, US+UK,), case-control study of fully-genotyped HCM gene carriers (n=73) without LVH we developed a CMR prediction rule for gene mutation carriage from a derivation cohort (n=53) and tested the rule in a separate validation cohort (n=20). *Microscope:* To evaluate the neotenal hypothesis we performed advanced morphological analysis of cardiac trabeculae, crypts and MV in a large sample (n=108) of wild-type (WT; NIMR:Parkes and C57BL/6) embryonic murine hearts from the time of ventricular septation (E14.5) till just before birth (E18.5), using high-resolution episcopic microscopy.

Results: In the preclinical HCM cohort, a total of 21 CMR variables were studied. Multivariable conditional logistic regression created the final model consisting of 4 independently predictive parameters (**Fig.1a**): elongated anterior mitral valve leaflets (AMVL); increased apical trabecular complexity (by fractal analysis); presence of crypts; and smaller normalized LV end-systolic volume ratios ($LVESVi_R$). A risk score of ≥ 2 predicted carriership with a high level of accuracy (~80%) in both derivation and validation cohorts (**Fig.1b**).
In WT mouse, as expected cardiac trabeculae regressed with development, but in addition the embryonic heart was also found to contain crypts which largely regressed by birth, supporting the neotenal hypothesis (**Fig.2a,b**; scale bars, 0.5 mm; *P <0.05, **P<0.001).

Conclusion: This work confirms the existence of a preclinical HCM phenotype and shows how measurement of these parameters across multiple centers, and their combination into a simple imaging rule, could be useful for the clinically important group of individuals who possess the uncertainty of a 50% pre-test probability of sarcomere gene mutation carriership. Embryological investigation in mouse supports the hypothesis that at least some of this preclinical phenotype - the trabeculae and crypts - may represent an incomplete neotenal state that is related to the sarcomeric protein mutations.

Fig 1a

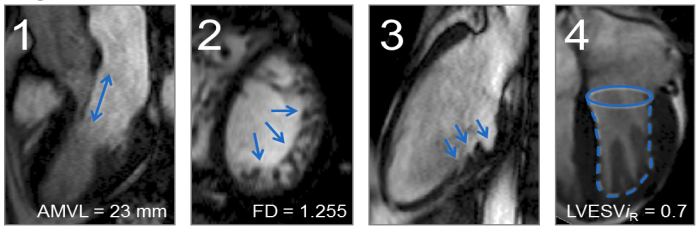
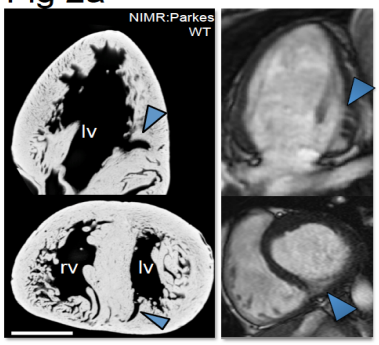


Fig 2a



Embryonic crypt in WT mouse

Adult human crypt/s by CMR

Fig 1b

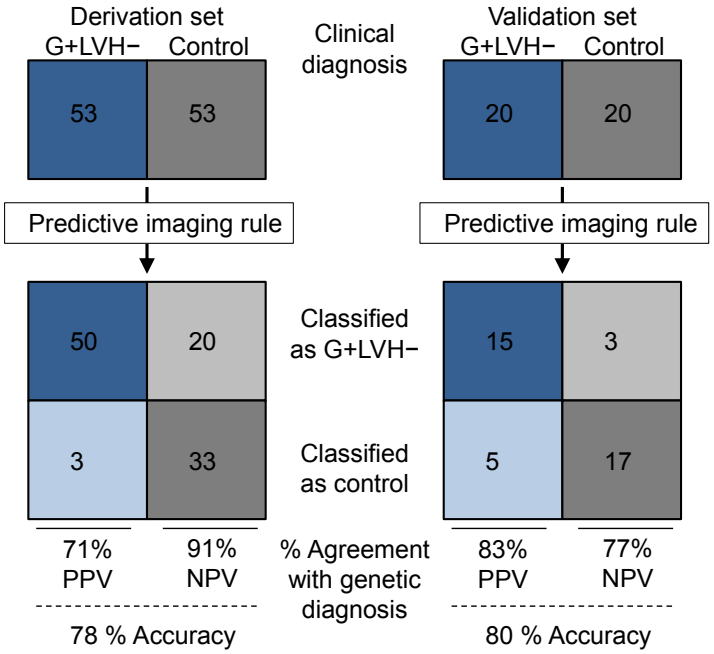
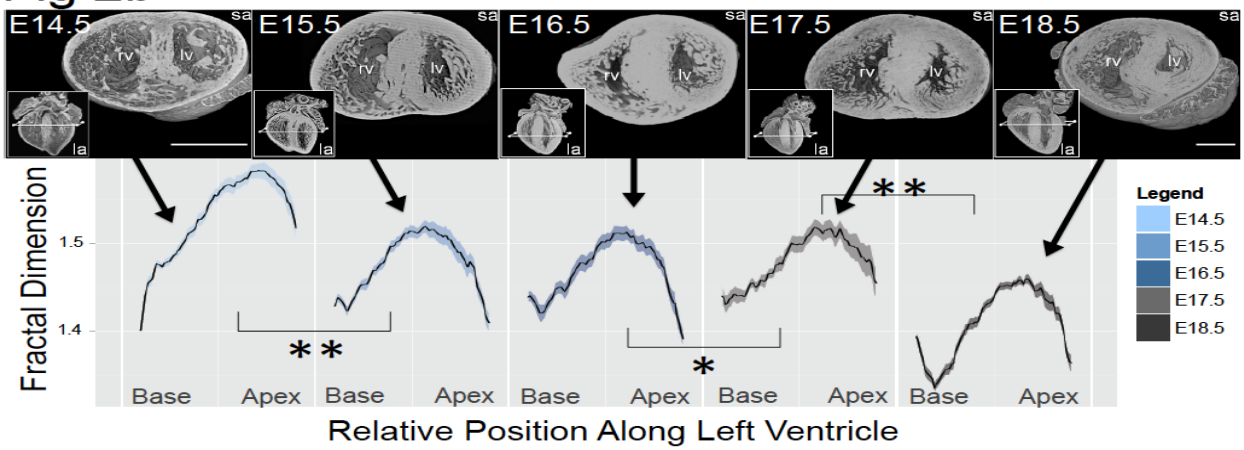


Fig 2b



Institutions: 1. University College London, London, UK; 2. The Heart Hospital, London, UK; 3. MRC National Institute for Medical Research, Mill Hill, UK; 4. Brigham and Women's Hospital, Boston, USA; 5. Harvard Medical School, Boston, USA; 6. University of Pennsylvania, Philadelphia, USA; 7. University College London, London, UK; 8. University of Oxford, Oxford, UK; 9. Great Ormond Street Hospital for Children, London, UK; 10. National Institutes of Health/Clinical Center, Maryland, USA