

## ORAL PRESENTATION

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# Advanced assessment of cardiac morphology and prediction of gene carriage by CMR in hypertrophic cardiomyopathy - the HCMNet/UCL collaboration

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## Background

Mycardial architectural abnormalities, have been identified in hypertrophic cardiomyopathy (HCM) gene mutation carriers without hypertrophy (G+LVH-). Some of these changes may be related to the underlying mutation, but whether they can predict gene carriage in relatives of HCM probands is unknown. Cardiac trabeculae may be prominent in overt HCM, suggesting they could form part of this constellation of abnormalities but previous techniques have not permitted more detailed study. We developed a fractal method for quantitation of trabeculae, tracked their development in embryonic mice and applied it to humans imaged by CMR. We hypothesize that fractal analysis may detect abnormal trabeculae in HCM mutation carriers before development of LVH and that a combination of cardiac architectural abnormalities could be used to predict gene carriage in HCM.

## Methods

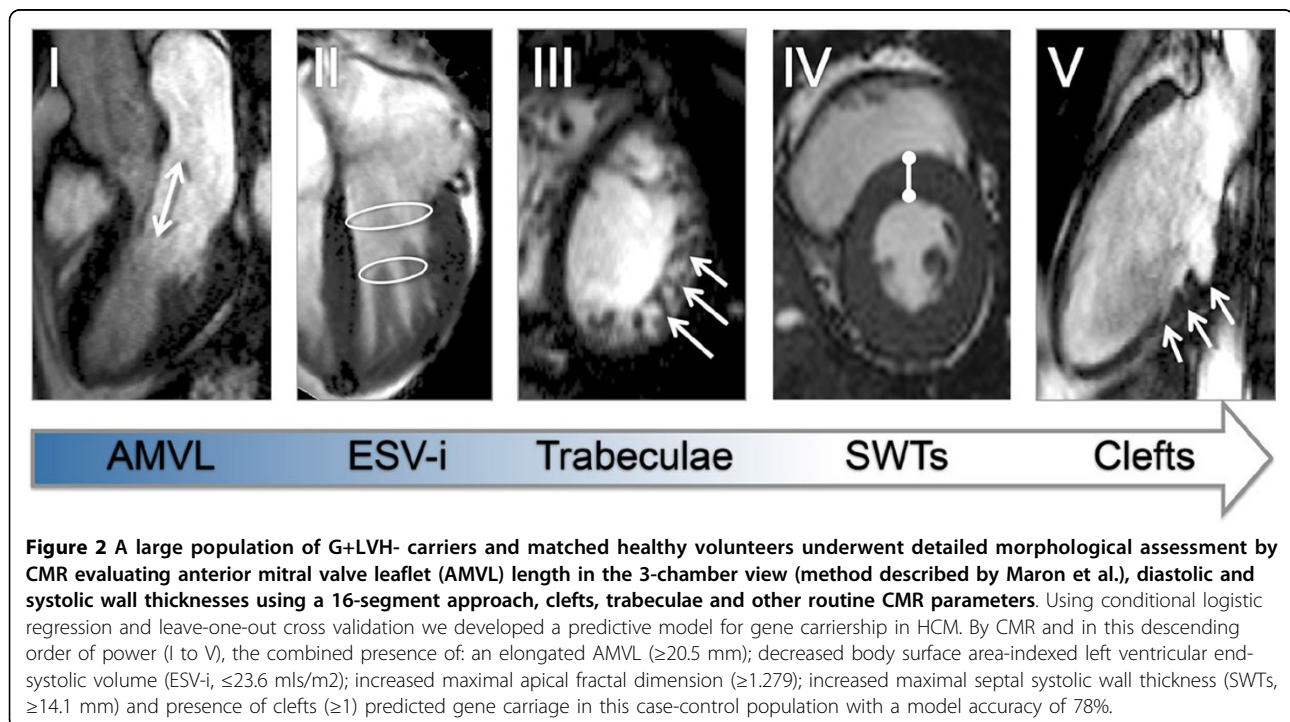
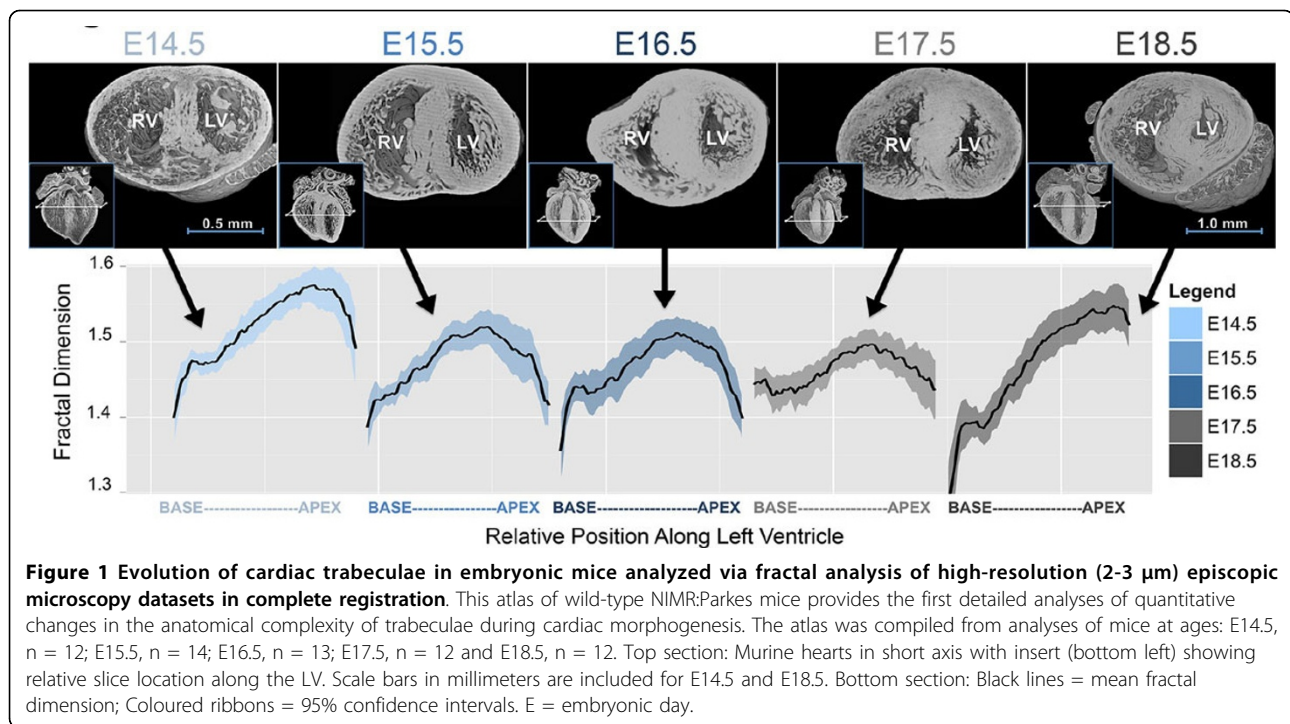
**TRABECULAE IN MOUSE EMBRYONIC DEVELOPMENT-63** Murine hearts were examined from the time of ventricular septation (E14.5) till just before birth (E18.5). Trabeculae were charted by fractal analysis of high-resolution episcopic microscopy images using a box-counting method. **HUMAN MORPHOLOGY-74** G+LVH- sarcomere mutation carriers (29 ± 13 yr [SD])

(51%M) were identified in 12 US-centers (HCMNet | n = 35) and UCL (n = 39). Subjects underwent CMR and fractal analysis. Results were compared with 111 overt HCM patients (G+LVH+ | n = 71; G-LVH+ | n = 40) and 136 matched controls (36 ± 16 yr | 63%M). We analyzed a single-center (UCL) G+LVH- case-control cohort to identify factors associated with gene carriage, evaluating anterior mitral valve leaflets (AMVL), wall thickness, clefts, trabeculae and other variables. We validated identified associations in the multi-center HCMNet cohort, and combined significant parameters into a model for predicting genetic carriage.

## Results

In mice a fractal atlas of trabecular development showed decreasing complexity across the basal LV (E14.5-18.5; p < 0.0001) while complexity in the mid/apical LV rose again just before birth (E17.5-18.5; p < 0.0001 | Figure 1). Contrasting the UCL case-control populations 5 differences were found and borne out in the validation cohort. Across the combined HCMNet/UCL cohort these were: 1) longer AMVL (22 ± 3 vs 20 ± 3 mm | p < 0.0001), 2) increased maximal-apical trabecular complexity (1.242 ± 0.07 vs 1.196 ± 0.05 | p < 0.0001), 3) increased maximal-septal systolic wall thickness (13 ± 3 vs 12 ± 2 mm | p = 0.02), 4) lower indexed-end-systolic LV volume

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( $23 \pm 6$  vs  $26 \pm 7$  mls/m<sup>2</sup> |  $p = 0.005$ ), and 5) presence of clefts ( $35$  vs  $7\%$  |  $p < 0.0001$ ). Conditional logistic regression provided a model containing these parameters, which predicted gene carriage with a high level of accuracy (78%; Figure 2).

### Conclusions

Fractal analysis applied to microscopy or CMR permits robust trabecular quantification. Trabecular complexity is increased in HCM gene mutation carriers even in the absence of LVH. Myocardial architectural abnormalities

are an early phenotype of sarcomere mutations; a pentad of cardiac architectural abnormalities by CMR exhibits potential for predicting genetic carriage in HCM.

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