The involvement of genes for human hypertrophic dilated cardiomyopathy to experimental polygenic cardiac hypertrophy

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Objectives: Genes implicated in monogenic human cardiac hypertrophy (CH) might also be involved in the more common polygenic forms. The Hypertrophic Heart Rat (HHR) is a unique normotensive model of spontaneous polygenic ventricular hypertrophy leading to cardiac failure and premature death. Our aim was to survey mRNA expression and genetic variants in genes previously associated with monogenic forms of dilated and hypertrophic cardiomyopathy in humans utilising the HHR.

Methods: We used Affymetrix GeneChip Rat Gene 1.0 ST arrays to measure whole-genome mRNA in left ventricles of HHR and its normal control, the Normal Heart Rat (NHR) (n=8 per group). We also performed whole-genome DNA sequencing of both strains using the HiSeq 2000 platform. We aligned and compared sequences to the Rat Genome Database v3.4 and identified four types of variants: SNPs, insertions and deletions (InDels), copy number variations (CNVs) and structural variants (SVs).

Results: We found 15 (Cryab, Dsg2, Lama4, Mybpc3, Myh6, Myh7, Myl2, Neun, Psen2, Rab26, Tnnc1, Tnn1, Tnn2, Tpm1, Ttn) of the initial known 40 candidate genes significantly differentially expressed in the HHR (FDR ≤ 0.05). Their fold change was small (≏1.3) consistent with a polygenic contribution. Overall, we found 182 variants unique to the HHR in our gene subset. Most variants were SNPs (n=101), followed by InDels (n=67), CNVs (n=12) and SVs (n=2). No major mutations typical of human monogenic cardiomyopathies were found. The majority of SNPs are located in non-coding regions (n=98) except for two variants in the coding region for the gene for troponin T type 2 (Tnn1) and one in its 3' untranslated region. Interestingly, both mutations in the coding region are synonymous and do not cause a change in the amino acid or protein sequence. Although the variants found in gene for Tnn1 are synonymous, silent mutations may alter gene expression levels by transfer RNA availability and influence phenotypically variability.

Conclusions: Our study is the first to show that genes involved in monogenic human forms of hypertrophy may also contribute through changed expression and subtle variants in DNA sequence to the common polygenic form of left ventricular hypertrophy.