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Abstract

Left ventricular mass (LVM) is a highly heritable trait and an independent risk factor for all-cause mortality. So far, genome-wide association studies have not identified the genetic factors that underlie LVM variation, and the regulatory mechanisms for blood-pressure-independent cardiac hypertrophy remain poorly understood. Unbiased systems genetics approaches in the rat now provide a powerful complementary tool to genome-wide association studies, and we applied integrative genomics to dissect a highly replicated, blood-pressure-independent LVM locus on rat chromosome 3p. Here we identified endonuclease G (Endog), which previously was implicated in apoptosis but not hypertrophy, as the gene at the locus, and we found a loss-of-function mutation in Endog that is associated with increased LVM and impaired cardiac function. Inhibition of Endog in cultured cardiomyocytes resulted in an increase in cell size and hypertrophic biomarkers in the absence of pro-hypertrophic stimulation. Genome-wide network analysis unexpectedly implicated ENDOG in fundamental mitochondrial processes that are unrelated to apoptosis. We showed direct regulation of ENDOG by ERR-α and PGC1α (which are master regulators of mitochondrial and cardiac function), interaction of ENDOG with the mitochondrial genome and ENDOG-mediated regulation of mitochondrial mass. At baseline, the Endog-deleted mouse heart had depleted mitochondria, mitochondrial dysfunction and elevated levels of reactive oxygen species, which were associated with enlarged and steatotic cardiomyocytes. Our study has further established the link between mitochondrial dysfunction, reactive oxygen species and heart disease and has uncovered a role for Endog in maladaptive cardiac hypertrophy.