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52 Genetic Loci Influencing Myocardial Mass

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ABSTRACT

BACKGROUND Myocardial mass is a key determinant of cardiac muscle function and hypertrophy. Myocardial depolarization leading to cardiac muscle contraction is reflected by the amplitude and duration of the QRS complex on the electrocardiogram (ECG). Abnormal QRS amplitude or duration reflect changes in myocardial mass and conduction, and are associated with increased risk of heart failure and death.

OBJECTIVES This meta-analysis sought to gain insights into the genetic determinants of myocardial mass.

METHODS We carried out a genome-wide association meta-analysis of 4 QRS traits in up to 73,518 individuals of European ancestry, followed by extensive biological and functional assessment.

RESULTS We identified 52 genomic loci, of which 32 are novel, that are reliably associated with 1 or more QRS phenotypes at $p < 1 \times 10^{-8}$. These loci are enriched in regions of open chromatin, histone modifications, and transcription factor binding, suggesting that they represent regions of the genome that are actively transcribed in the human heart. Pathway analyses provided evidence that these loci play a role in cardiac hypertrophy. We further highlighted 67 candidate genes at the identified loci that are preferentially expressed in cardiac tissue and associated with cardiac abnormalities in *Drosophila melanogaster* and *Mus musculus*. We validated the regulatory function of a novel variant in the *SCN5A/SCN10A* locus in vitro and in vivo.

CONCLUSIONS Taken together, our findings provide new insights into genes and biological pathways controlling myocardial mass and may help identify novel therapeutic targets. (J Am Coll Cardiol 2016;68:1435-48)

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