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Functional genetic variants in chromogranin a and their role in cardiovascular and metabolic diseases

Nitish R Mahapatra

Department of Biotechnology, Bhupat and Jyoti Mehta School of Biosciences, Indian Institute of Technology Madras, Chennai, India

Correspondence: Nitish R Mahapatra, Department of Biotechnology, Bhupat and Jyoti Mehta School of Biosciences, Indian Institute of Technology Madras, Chennai 600036, India, Email nmahapatra@iitm.ac.in

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Chromogranin A (CHGA), a ~50 kDa soluble, acidic glycoprotein present abundantly in secretory vesicles of endocrine, neuronal and neuroendocrine cells, is co-stored and co- secreted with catecholamines. CHGA plays a crucial role in the biogenesis of these secretory vesicles. CHGA is also a pro-hormone that generates bioactive peptides including catecholamine release inhibitory/ anti-hypertensive peptide catestatin (CST), dysglycemic peptide pancreastatin (PST), vasodilator vasostatin, parathormone release inhibitory peptide parastatin (PRST) and myocardial beta-adrenergic-like agonist serpinin. Plasma CHGA levels are elevated in many cardiovascular diseases including myocardial infarction and acute coronary syndrome. On the other hand, plasma CST level is diminished in essential hypertension. Consistent with these observations, Chga knockout mice displays elevated blood pressure that gets rescued by expression of human orthologue or by administration of human CST peptide.

Very recently, it has been reported that CHGA-to-CST conversion is diminished in heart failure patients and this is associated with clinical outcomes of acute heart-failure. In view of these findings, CHGA is emerging as a crucial regulator of cardiovascular diseases. We resequenced the CHGA locus (~1.2 kb promoter and exonic regions) in an Indian population to identify functional polymorphisms that may govern CHGA expression and function.

Eight common and one novel single nucleotide polymorphisms (SNPs) were detected in the promoter region; their allele and haplotype frequencies were significantly different from that of the European population. Linkage disequilibrium (LD) analysis suggested strong LD among SNPs at the -1106, -1014, -988 and -89 bp positions and between the -1018 and -57 bp positions. Five major promoter haplotypes were predicted; the haplotypes showed differential promoter activities in neuronal cells. Of note, the haplotype 2 (containing variant T alleles at -1018 and -57 bp) exhibited the highest promoter activity as compared to all other haplotypes in the population. Computational, cellular and molecular analysis revealed that stronger binding of the transcription factor c-Rel with the haplotype 2 underlies the enhanced expression of CHGA. In corroboration, individuals carrying haplotype 2 genotype showed higher plasma CHGA levels; these subjects also displayed elevated BMI, diastolic blood pressure and plasma glucose levels suggesting a functional role of this haplotype in conferring cardiometabolic risk. We also observed that a variant within the CST domain (viz. Gly364Ser) and a variant within the PST domain (viz. Gly297Ser) enhanced the risk for hypertension and type 2 diabetes respectively in the Indian population. Taken together, functional genetic variants of CHGA emerge as novel regulators of cardiovascular and metabolic disease states.