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Discovery of functional genetic variations in Indian populations and their associations with cardiovascular/metabolic diseases

Dr. Mahapatra's laboratory at IIT Madras discovered a number of genetic variants in the chromogranin A gene that has emerged as new regulator of cardiovascular and metabolic diseases. Chromogranin A (CHGA) undergoes post-translational modifications and generates bioactive peptides such as anti-hypertensive/cardioprotective catestatin (CST) and dysglycemic pancreastatin (PST). He undertook large scale case-control studies in Indian populations (using several thousand individuals from North and South India). Linkage disequilibrium analysis and genetic association studies identified several genetic variations in chromogranin A locus that enhance the risk for cardiovascular/metabolic disorders in Indian populations. Furthermore, using various experimental (cellular/ biochemical/ biophysical/ physiological assays), and computational (molecular modelling, molecular dynamic simulations, docking of peptides with their receptors) his research group demonstrated that these variants alter the expression of chromogranin A or potency of catestatin /pancreastatin peptides.

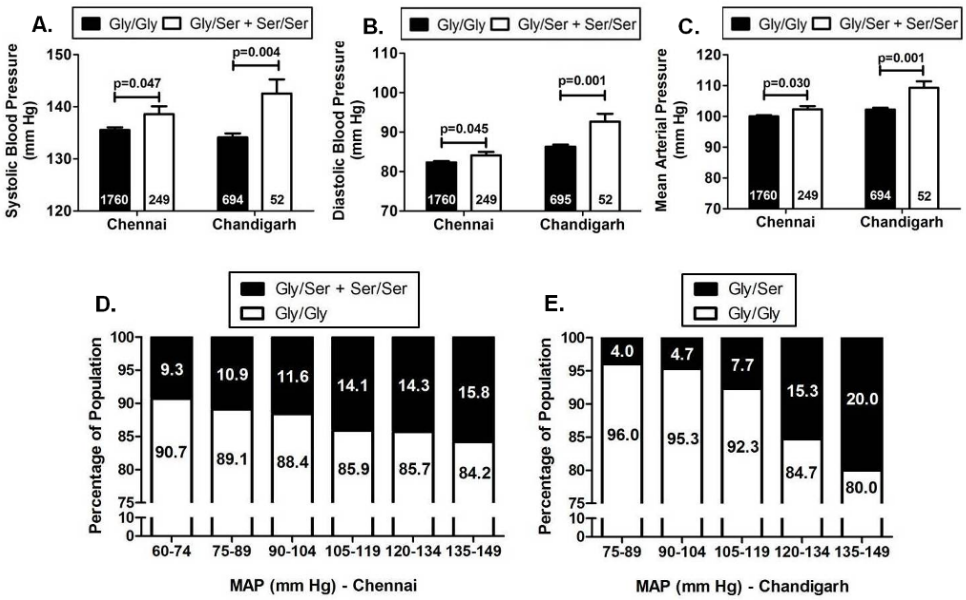

Figure 1. Allele-specific associations of the CST Gly364Ser variation with blood pressure. Panels A, B and C: Data are shown as mean ± SE. SBP (A), DBP (B) and MAP (C) levels in the carriers of 364Ser allele were higher (analyzed by independent samples t-test using SPSS version 21.0) than the wild-type individuals in the overall Chennai and Chandigarh populations. **Panels D and E:** Data are shown as percentage. The percentage of individuals harboring the 364Ser allele showed an increase with increase in the range of the MAP levels in both the Chennai (D) and Chandigarh (E) populations.

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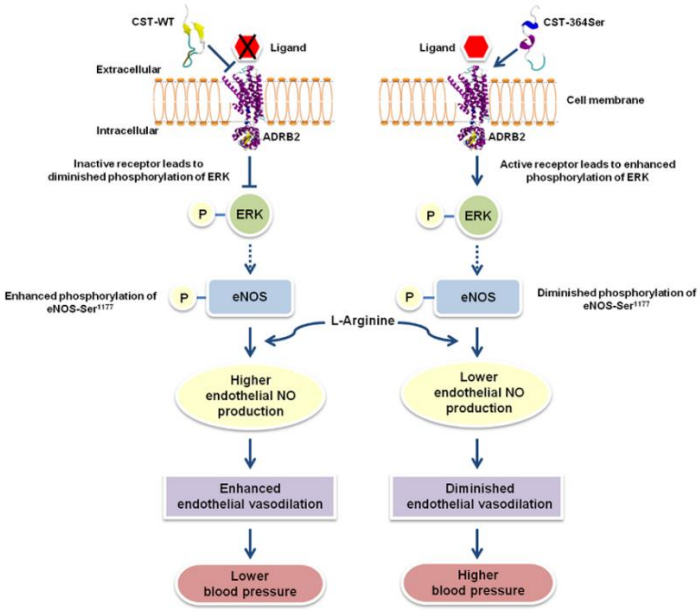

Figure 2. A schematic representation of the mechanistic basis for the effects of CST peptides on blood pressure. The CST-364Ser peptide does not interact at the ligand binding site of ADRB2 unlike CST-WT owing to differences in their secondary structures. Their differential interactions with ADRB2 result in diminished antagonization of ADRB2 and enhanced activation/ phosphorylation of ERK by CST-364Ser. The altered ERK activation between the CST peptides may result in diminished phosphorylation of eNOS-Ser^{1177} and consequently lower eNOS activity in the case of CST-364Ser. These cellular/molecular processes lower the NO levels in vascular endothelial cells in the carriers of CST 364Ser allele leading to endothelial dysfunction and thereby increasing their risk for hypertension.

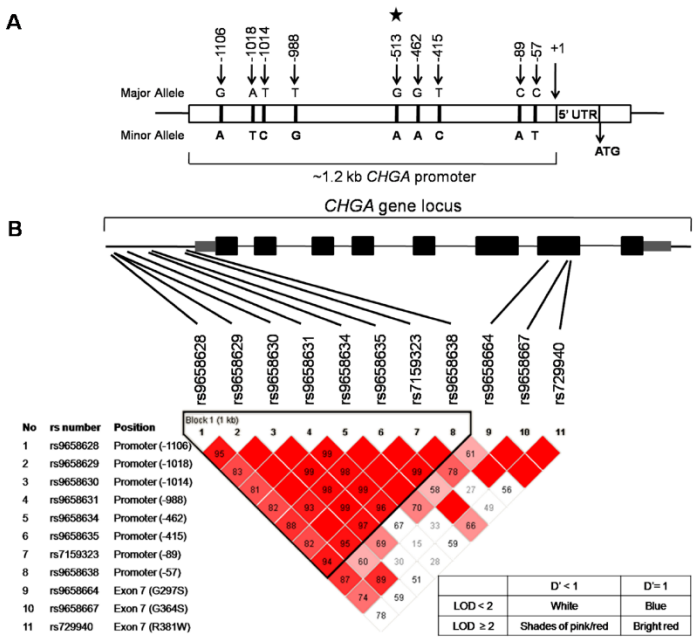

Figure 3. *CHGA* polymorphisms and linkage disequilibrium (LD). **(A)** Schematic showing the polymorphisms identified in *CHGA* promoter in an Indian population. The G-513A indicated by a 'star' is a novel polymorphism. **(B)** LD plot of common polymorphisms in *CHGA* promoter and exon 7 region. Pairwise LD values were plotted between common SNPs in the *CHGA* promoter and exon 7 region (coding for catestatin, pancreastatin and parastatin) of CHGA using Haploview 4.2. D': Coefficient of LD; LOD: log of the likelihood odds ratio.

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Similarly, Dr. Mahapatra's laboratory identified functional variants in the regulatory region of matrix metalloproteinases (viz. matrix metalloproteinase 7 and 8) and established that these variants alter the risk factors for cardiometabolic disorders.

Table 1. Association of MMP7 -181A/G polymorphism with hypertension risk in Indian populations.

MMP7 Promoter Genotype	Chennai Population				Chandigarh Population			
	Logistic Regression (Unadjusted), n=1501		Logistic Regression (Age, Sex, and BMI Adjusted), n=1453		Logistic Regression (Unadjusted), n=949		Logistic Regression (Age and Sex Adjusted), n=949	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
AA	1 (ref)	…	1 (ref)	…	1 (ref)	…	1 (ref)	…
AG	1.60 (1.25–2.04)	1.6×10^{-4}	1.60 (1.25–2.06)	2.4×10^{-4}	1.49 (1.12–1.97)	0.006	1.52 (1.11–2.09)	0.010
GG	0.99 (0.75–1.33)	0.98	1.01 (0.75–1.36)	0.94	1.14 (0.78–1.66)	0.49	1.31 (0.86–2.01)	0.210
AG+GG	1.37 (1.09–1.73)	0.006	1.39 (1.09–1.75)	0.007	1.38 (1.06–1.80)	0.017	1.46 (1.09–1.98)	0.013

BMI indicates body mass index; CI, confidence interval; MMP7, matrix metalloproteinase-7; and OR, odds ratio.

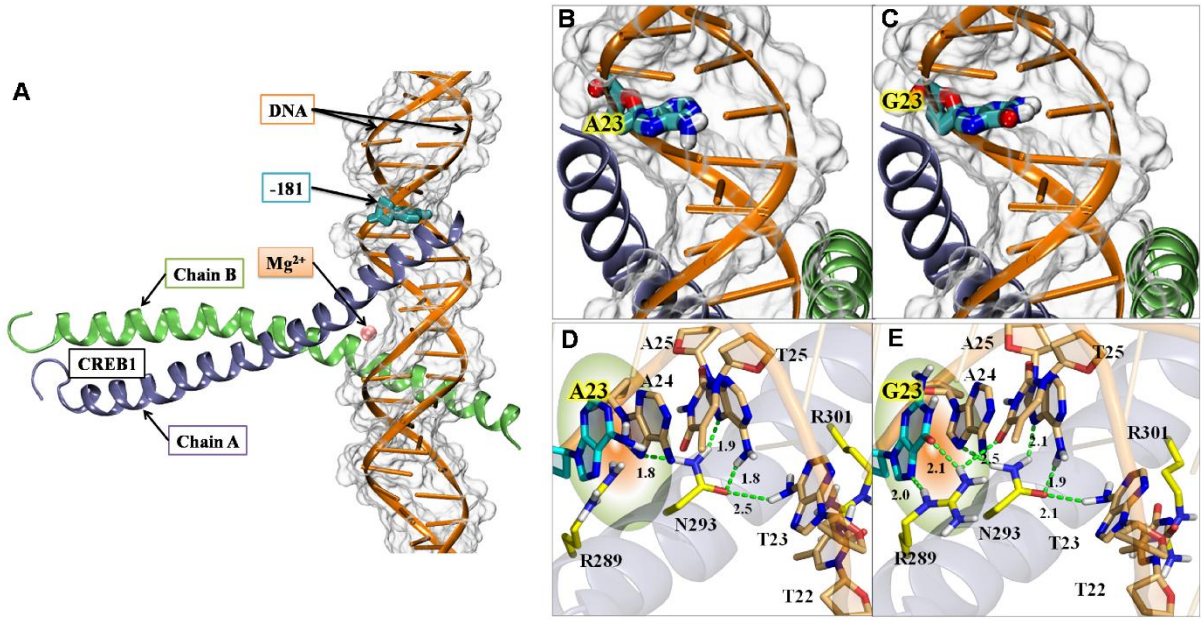

Figure 4. Schematic diagram of interactions of *MMP7*-promoter DNA with CREB1 transcription factor. **(A)** Representative energy minimized model of CREB1:wild-type *MMP7* complex rendered in new cartoon representation. DNA is shown in orange color; CREB1-chain A and CREB1-chain B are shown in ice-blue and green colors, respectively. DNA is shown in transparent white surface view as well. Position of the -181 bp nucleotide and Mg^{2+} has been indicated. **(B)** Positioning of the key nucleotide -181A (labelled as A23) in wild-type promoter. **(C)** Positioning of key nucleotide -181G (labeled as G23) in the mutant promoter. **(D)** and **(E)** Comparison of wild-type and mutant *MMP7*-promoter DNA interactions with CREB1 in enlarged view. Amino acids are indicated by single letter codes and based on their positions in the CREB1-chain A. Amino acids and nucleotides are rendered in licorice and colored atom wise; C: light orange, N: blue, O: red, H: white. Hydrogen bonds are shown in green dotted lines. The mutant promoter (E) involves several additional hydrogen bonds as compared to the wild-type promoter (D) suggesting stronger interactions with CREB1.

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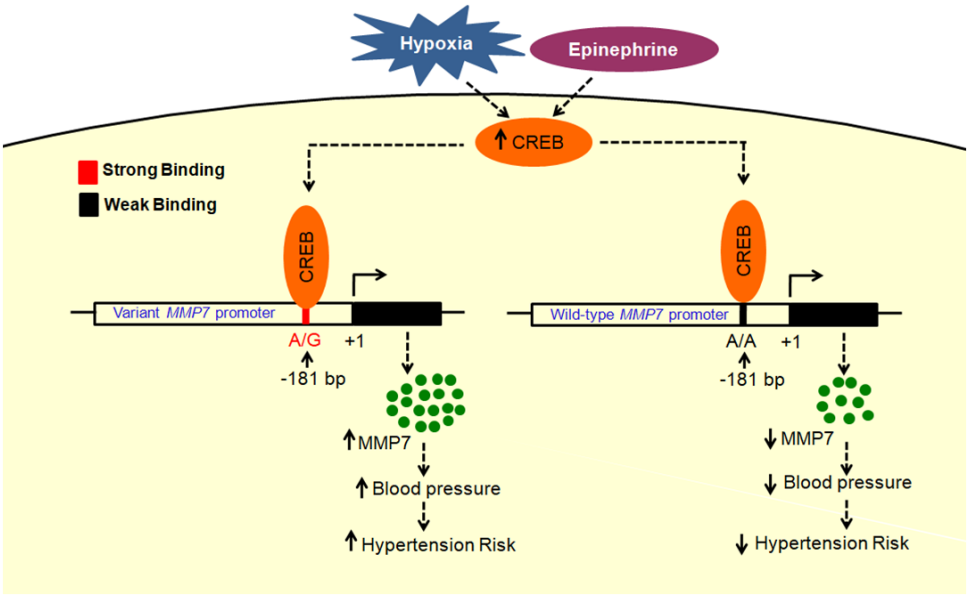

Figure 5. A schematic illustration of the plausible mechanistic basis for the increased hypertension risk conferred by the *MMP7* -181G promoter variant. The *MMP7*-181G promoter showed higher promoter activity consistently among different cell lines due to transcriptional activation by CREB. Pathophysiological conditions (viz. catecholamine excess and hypoxia) further increase the promoter activity of the *MMP7* -181G construct in an allele-specific manner by activating CREB and inducing its phosphorylation. The higher promoter activity of *MMP7* -181G construct corroborates with the elevated levels of plasma MMP7 observed in -181AG individuals which, in turn, positively correlates with blood pressure suggesting that these heterozygous individuals may be at a higher risk for hypertension and its complications.

These studies provided new molecular mechanisms contributing to cardiovascular diseases and have implications for development of diagnostic and therapeutic strategies for management of these diseases.

References:

1. Subramanian L, Maghajothi S, Singh M, Kesh K, Ananthamohan K, Sharma S, Khullar M, Victor SM, Swarnakar S, Asthana S, Mullasari AS, **Mahapatra NR**. 2019. A common tag nucleotide variant in *MMP7* promoter increases risk for hypertension via enhanced interactions with CREB (Cyclic AMP Response Element-Binding Protein) transcription factor. ***Hypertension*** 74:1448-1459. ***(Impact factor: 10.19)***
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