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A functional mmp7 promoter polymorphism increases risk for hypertension in indian populations

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MMP7 (Matrilysin), the smallest known member of the matrix metalloproteinase family of enzymes, is involved in the breakdown of extracellular matrix proteins during physiological processes like embryonic development and tissue remodelling. Knockdown of MMP7 in spontaneously hypertensive rat models attenuated hypertension and variants in the MMP7 gene promoter have been studied in several cancers and hypercholesterolemia. In this study, we probed for the association of a widely reported promoter polymorphism (-181A/G; rs11568818) with hypertension in an urban Chennai population (n=1425). The AG (heterozygous variant) genotype showed a significant risk of association with hypertension when compared to the AA (wild-type) genotype (OR=1.645, 95% CI = 1.290-2.098; p=3x10-5) with the individuals of AG genotype displaying ~5mm/~3mm Hg higher systolic blood pressure (SBP)/ diastolic blood pressure (DBP) than the individuals of AA genotype. The study was also replicated in a population (n=808) from Chandigarh (OR=1.663, 95% CI =1.140-2.425; p=0.008). Transient transfection of the MMP7 promoter-luciferase reporter constructs established that the -181G allele confers higher promoter activity than the -181A allele. Computational and experimental analyses revealed a stronger binding site for the transcription factor CREB in case of the -181G allele. Pathophysiological stimuli like hypoxia and catecholamine excess enhanced the promoter activity of the -181G allele further. The higher promoter activity of „G" allele also translated to increased MMP7 protein levels in vitro. In conclusion, the -181G allele of MMP7 promoter polymorphism (rs11568818) is shown to be associated with elevated gene expression and blood pressure thereby increasing the risk for hypertension.

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