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HYPERTENSION

Role of *ARHGAP42* in hypertension

> expression of [ARHGAP42] might act as a negative feedback mechanism to limit excessive vessel constriction

A new study suggests a role of the *ARHGAP42* genotype in determining risk of hypertension. Joan Taylor, Christopher Mack and colleagues previously identified ARHGAP42 as a Rho GTPase-activating protein that is selectively expressed in smooth muscle cells (SMCs) and controls blood pressure (BP) by regulating vascular tone.

The researchers have now identified a regulatory element in *ARHGAP42* that encompasses the BP-associated single nucleotide polymorphism, rs604723, and has SMC-selective activity. CRISPR/Cas9-mediated deletion of this regulatory element significantly reduced endogenous ARHGAP42 expression in human aortic SMCs. Moreover, the presence of the minor T allele at rs604723 enhanced the activity of the regulatory element. "The presence of this allele created a low-affinity binding site for serum response factor, which has previously been implicated in SMC-specific gene expression," says Mack.

ARHGAP42 expression in vascular SMCs was upregulated by cell stretch, hypertension, and RhoA-dependent agonists, suggesting that expression of this GTPase might act as a negative feedback mechanism to limit excessive vessel constriction. Consistent with this hypothesis, *Arhgap42*-deficient mice showed increased susceptibility to DOCA-salt-mediated hypertension.

Finally, the researchers showed that the minor T allele of *ARHGAP42* was associated with reduced diastolic BP in patients with untreated borderline hypertension. "Genotypic analysis of approximately 1,000 individuals from several additional clinical cohorts suggested that the low frequency of the minor *ARHGAP42* allele in African Americans might contribute to the susceptibility of this population to the development of hypertension," comments Taylor. "Our findings could perhaps lead to the development of personalized treatment options for hypertension based on *ARHGAP42* genotype."

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