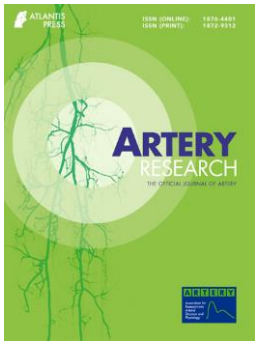

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Adducin and its relation to cardiovascular system

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KEYWORDS
Adducin;
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Stroke

Abstract Adducin is a cytoskleton protein, which functions within the cells as a heterodimer composed of a combination of three subunits, α, β and γ. Each of these subunits is coded by genes (*ADD1*, *ADD2*, *ADD3*) mapping to different chromosomes. Mutation in *ADD1 Gly460Trp* polymorphism is associated with increased Na^+K^+-ATPase activity and increased renal tubular sodium reabsorption, which leads to salt-sensitive hypertension. A number of studies focused on possible association between these genes alone, or together with the interaction with other modulatory genes or with the environment, in relation to cardiovascular phenotypes. Variations in adducin genes were shown to modulate intermediate phenotypes such as arterial distensibitity, carotid IMT and left ventricle diastolic function. Moreover, some studies demonstrated an association between adducin genes and coronary artery disease, stroke and mortality. We showed that genetic variations in *ADD1*, *ADD3* and angiotensin II receptor type-1 receptor interactively influenced the elastic properties of brachial and femoral arteries. Concerning the antihypertensive treatment, it was speculated that carriers of mutated *ADD1 460Trp* allele might benefit from diuretic use, however the present findings on this subject remain inconsistent. In conclusion, adducin might play an important role in the cardiovascular system.

Introduction

Adducin is a heterodymeric cytoskeleton protein, the three subunits are encoded by genes (*ADD1*, *ADD2*, *ADD3*) mapping to three different chromosomes. Mutation of the α-adducin gene (*ADD1*) entails increased Na^+K^+-ATPase activity,[1,2] and increased renal tubular reabsorption.[3] Variation in the Na^+K^+-ATPase activity and in the intracellur Na^+ concentration might influence sodium-dependent transmembranous Ca^{2+} transport in vascular smooth muscle cells and via this mechanism might affect arterial tone.[4]

Previous studies in a randomly selected Flemish population (FLEMENGHO) demonstrated that an interaction between the genes encoding *ADD1* (*Gly460Trp* polymorphism), the angiotensin-converting enzyme (*ACE*) and the angiotensin II type-1 receptor influenced the distensibility, cross-sectional compliance, and intima-media thickness of the femoral artery.[5,6] Cwynar et al. reported interaction between the *ADD1 Gly460Trp* polymorphism and the *A386G* polymorphism in the γ-adducin subunit (*ADD3*). Peripheral and central pulse pressures were higher in carriers of both the *ADD1 Trp* allele and the *ADD3 G* allele.[7] Moreover, in the prospective study from the FLEMENGHO population, the combination of *ACE DD* homozygosity and mutated *ADD1*, worsened cardiovascular prognosis to a similar extent as classical risk factors.[8]

This review article summarizes our results related to association between adducin polymorhisms and arterial

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properties and puts these into perspective against other published studies.

Adducin and arteries

Previous findings of the FLEMENGHO population showed interactions between the *ADD1*, *ACE*, and aldosterone synthase genes in relation to femoral intima-media thickness[5] and carotid and femoral distensibility.[6] We hypothesized that arterial properties might be related not only to interaction of *ADD1* with *ACE*, but also interaction of *ADD1* with two other adducin subunits genes or the genes encoding various components of the renin–angiotensin system. We addressed this question in randomly selected participants of the FLEMENGHO study.

The key finding of our study was that brachial diameter decreased ($P = 0.0001$), while brachial distensibility increased with the *ADD3 G* allele, and that these associations were confined to *ADD1 GlyGly* homozygotes (Fig. 1).[9] In the family-based analyses, we did not find any evidence for population stratification ($0.07 \leq P \leq 0.96$). Transmission of the *ADD3 G* allele was associated with a smaller brachial diameter in all 342 informative offspring ($P = 0.0085$) as well as in offspring homozygous for *ADD1 Gly* allele ($n = 209$; $P = 0.018$). *ADD1* and *ADD2*, alone or in combination with each other, were not associated with the arterial properties in the three arterial beds. This was also true for *ADD1* and *ADD3* in relation to the carotid and femoral phenotypes.[9]

Moreover, we observed that femoral cross-sectional compliance ($P = 0.020$) and distensibility ($P = 0.055$) were higher in *AT1R C* allele carriers than in *AT1R AA* homozygotes, but that this association was only observed in the presence of the mutated *ADD1 Trp* allele, and not in *ADD1 GlyGly* homozygotes ($P \geq 0.16$).[10] In the family-based analyses, transmission of the *AT1R C* allele was associated with higher femoral distensibility in offspring carrying the mutated *ADD1 Trp* allele ($n = 115$, $P = 0.022$)[10] (Fig. 2)

Our epidemiological study only allows speculation about the reasons why there might be an association between the properties of the brachial artery, a small muscular artery, and the *ADD3 A386G* polymorphism. One possible mechanism is that the polymorphism might affect the neurogenic tone of vascular smooth muscle cells. Indeed, in rat models, increased blood pressure was associated with a decrease in the hypothalamic levels of γ-adducin mRNA and protein.[11,12] Furthermore, inhibition of γ-adducin by intracellular delivery of γ-adducin-specific antibodies increased the neuronal firing rate possibly via regulation of Na^+,-K^+-ATPase.[11] On the other hand, given that the phenotypes representative of two other arterial segments did not shown any association with the adducin SNPs, suggests that local mechanisms in the brachial artery, rather than the central nervous system, might underlie the demonstrated findings.

There is an apparent discrepancy between our analyses in which compliance of femoral artery was lower in the *AT1R AA* homozygotes carrying *ADD1 Trp* allele, whereas in other analyses of hypertensive subjects, arterial stiffness assessed as aPWV was increased with *AT1R C* allele.[13,14] However, these studies cannot be compared. Compliance of artery is a parameter measured locally at one arterial site, while aPWW reflects characteristics of arterial segment between two sites of measurements, e.g. carotid and femoral artery. Elastic aorta and muscular femoral artery have different properties.[15] Moreover, observations collected in a general population should not be extrapolated to hypertensive patients. Indeed, the aforementioned association between aPWV and *AT1R C* allele was found only

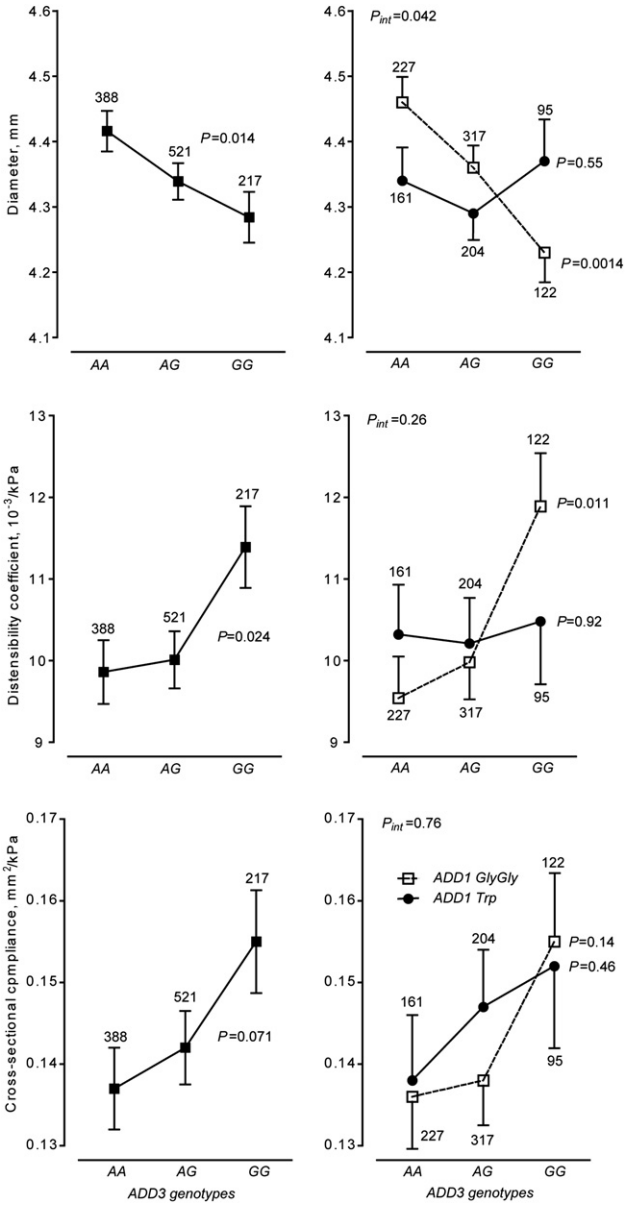

Figure 1 Diameter, distensibility and cross-sectional compliance of brachial artery in relation to *ADD1 Gly460Trp* and *ADD3 A386G* polymorphisms The analyses were adjusted for the observer, sex, age, body mass index, mean arterial pressure, heart rate, smoking, alcohol intake and the use of antihypertensive drugs and account for family clusters. Values are least square means ± SEs. The number of subjects contributing to each plotted point are given. *P*-values are linear trend across the *ADD3* genotypes. P_{int} indicates the significance of the 2-way interaction between *ADD1* and *ADD3*.

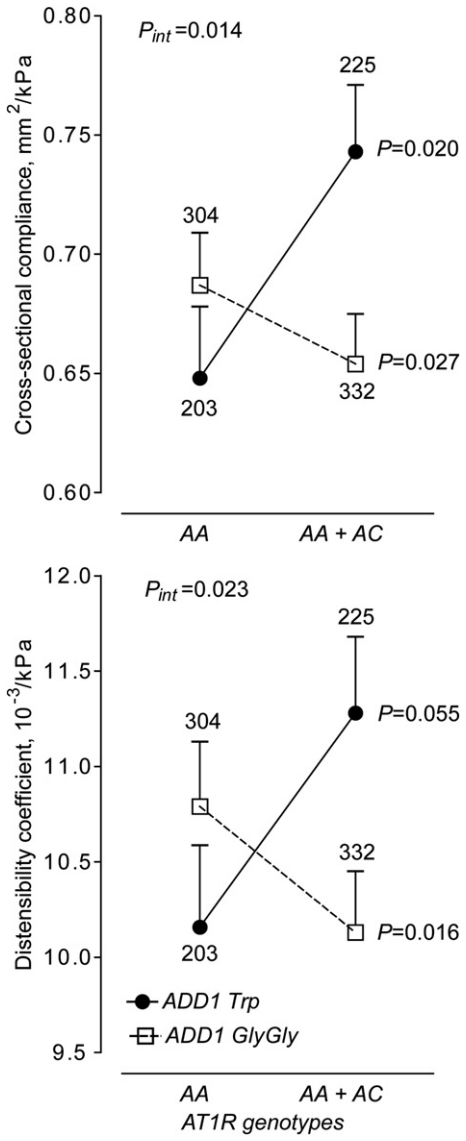

Figure 2 Femoral cross-sectional compliance and distensibility in relation to the *ADD1* and *AT1R* genotypes The analyses were adjusted for the same covariates as in Fig. 1. Values are least square means ± SEs. The number of subjects contributing to each plotted point are given. *P*-values denote the siginificance of the difference between *AT1R* genotypes. P_{int} indicates the significance of the interaction between *ADD1* and *AT1*R.

in hypertensive, but not in normotensive, individuals.[13] Finally, we demonstrated the effect of *AT1R C* allele only in carriers of mutated *ADD1 Trp* allele, which implicates gene—gene interaction.

Adducin and cardiovascular complications

In the FLEMENGHO participants, the left ventricular diastolic relaxation assessed by tissue Doppler imaging was modulated by genetic variations in *ADD1* and *ADD3*.[16] Below the age of 50 years, the lateral Ea/Aa ratio was higher in *ADD1 Trp* allele carriers than in *GlyGly* homozygotes, particularly in the presence of *ADD3 GG* homozygosity. In older subjects, these phenotype-genotype associations were not significant.[16] In several studies, hypertensive *ADD1 Trp* allele carriers[17—20] had increased risk of coronary artery disease. Moreover, in black patients with coronary artery disease, *ADD1* variant was associated with an 8-fold excess risk of all-cause death.[19]

In 6471 participant of the prospective Rotterdam study,[20] *ADD1* variant carriers had increased risk of ischemic stroke (hazard ratio [HR], 1.29; 95% CI, 1.02 to 1.63), and this was true mainly in hypertensive subjects (HR, 2.32; 95% CI, 1.68 to 3.21). Moreover, in healthy Dutch women free from previous cardiovascular disease,[21] the *ADD1 Trp* polymorphism was related to risk of stroke in later life. The risk of ischemic stroke was 10.9-fold higher among women with systolic hypertension compared to normotensive *GlyGly* homozygotes.[21]

An increased risk of stroke or coronary artery disease associated with variant *ADD1* allele seems to be more pronounced in hypertensive subjects, in whom we can expect the role of gene—gene interaction or gene—environmental interaction. Indeed, in a FLEMENGHO population the combination of *ACE DD* homozygosity and mutated *ADD1* worsened the cardiovascular prognosis to a similar extent as classical risk factors.[8] In *ADD1 Trp* allele carriers, the multivariate-adjusted hazard ratios associated with *ACE DD* versus *I* were 1.72 ($P = 0.007$) for total mortality, 2.35 ($P = 0.02$) for cardiovascular mortality, 2.02 ($P = 0.005$) for all cardiovascular events, and 2.59 ($P = 0.03$) for heart failure. In contrast, these hazard ratios did not reach significance in *ADD1 GlyGly* homozygotes ($0.08 \leq P \leq 0.90$).[8]

Adducin and use of diuretics

ADD1 Gly460Trp polymorphism was associated with an increased renal sodium reabsorption[3] and was linked to salt-sensitive hypertension.[22] Thiazide diuretics promote renal sodium excretion. This action of diuretics counteracts the biological effect of the α-adducin polymorphism. Therefore, in *ADD1 Trp* carriers, it is supposed they can benefit from use of diuretics. This question was explored in several studies.[19,23—26] However, results of these studies are inconsistent. In a population based case-control study, the *Trp* allele was associated with a lower risk of myocardial infarction in users of diuretics compared with users of other blood pressure lowering medication.[23] In GENHAT, a genetic study[24] conducted within a randomized clinical trial, women carrying *Trp* allele who used chlorthalidone had a greater risk of myocardial infarction, whereas men did not. The other three studies found no interaction between the α-adducin gene and the use of diuretics on the prevention of myocardial infarction or stroke.[19,25,26] These conflicting results suggest that *ADD1* genotype guided therapy with diuretics may not be a clinically or economically useful method to improve antihypertensive therapy.

Conclusion

From three genes encoding the adducin subunits, *ADD1 Gly460Trp* polymorphism is the most important for cardiovascular system. Mutation in *ADD1* gene modulates arterial

properties, diastolic function of left ventricle, and is associated with higher risk of stroke, coronary artery disease and increased mortality rate. Hypertensive background is important when considering effect of *ADD1 Trp* allele on stroke or coronary artery disease. Therefore, interaction of adducin with other genes or with environmental factors should be considered when study effect of this polymorphism on cardiovascular system.

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