Genome-wide association study of L-arginine and dimethylarginines reveals novel metabolic pathway for symmetric dimethylarginine.

Abstract:
Dimethylarginines (DMA) interfere with nitric oxide formation by inhibiting nitric oxide synthase (asymmetrical DMA [ADMA]) and L-arginine uptake into the cell (ADMA and symmetrical DMA [SDMA]). In prospective clinical studies, ADMA has been characterized as a cardiovascular risk marker, whereas SDMA is a novel marker for renal function and associated with all-cause mortality after ischemic stroke. The aim of the current study was to characterize the environmental and genetic contributions to interindividual variability of these biomarkers. This study comprised a genome-wide association analysis of 3 well-characterized population-based
cohorts (Framingham Heart Study [FHS; n=2992], Gutenberg Health Study [GHS; n=4354], and Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Study [MONICA]/Cooperative Health Research in the Augsburg Area, Augsburg, Bavaria, Germany [KORA] F3 [n=581]) and identified replicated loci (DDAH1, MED23, Arg1, and AGXT2) associated with the interindividual variability in ADMA, l-arginine, and SDMA. Experimental in silico and in vitro studies confirmed functional significance of the identified AGXT2 variants. Clinical outcome analysis in 384 patients of the Leeds stroke study demonstrated an association between increased plasma levels of SDMA, AGXT2 variants, and various cardiometabolic risk factors. AGXT2 variants were not associated with poststroke survival in the Leeds study or were they associated with incident stroke in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. These genome-wide association study support the importance of DDAH1 and MED23/Arg1 in regulating ADMA and l-arginine metabolism, respectively, and identify a novel regulatory renal pathway for SDMA by AGXT2. AGXT2 variants might explain part of the pathogenic link between SDMA, renal function, and outcome. An association between AGXT2 variants and stroke is unclear and warrants further investigation.