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Abstract

Integrated Analysis of Genomic and GWAS Data to Identify Candidate Genes for Genetic Studies in Flavonoids and Vascular Health: Path to Precise Nutrition for (Poly)phenols †

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Abstract: Good vascular function is one of the key determinants of a healthy heart and preserved neurofunction in advanced age. Previous studies demonstrated vasculoprotective effects of flavonoids, but also inter-individual variability in their action. Several factors have been identified as key determinants of this inter-individual variability, which include sex, age, ethnicity, body mass index, health status, gut microbiome, and genetic factors. Of these, genetic factors are the least studied. The aim of this study was to identify genes that are associated with the vascular health effects of flavonoids and whose polymorphisms could explain inter-individual variability in response to intake of these plant food bioactives. Applying predetermined literature search criteria, we identified five human intervention studies reporting positive effects of flavonoids on vascular function together with global genomic changes analyzed using microarray techniques. Genes involved in vascular dysfunction were identified from genome-wide association studies (GWAS), followed by integrative analyses, functional analyses, and literature search, to identify priority candidate genes for future nutrigenetic studies in flavonoids and vascular health. By extracting data from the eligible human intervention studies, we obtained five sets of differentially expressed genes (DEGs) with n = 1693; 717; 554; 2231; and 1401 genes, or a total number of 5807 genes. The number of identified URs varied across the studies, from 227 to 1407 i.e., n = 227; 503; 508; 1407, and 993. Searching of the GWAS Catalog revealed 493 genes associated with vascular dysfunction. Further, an integrative analysis of transcriptomic data with GWAS genes identified 106 candidate DEGs and 42 candidate URs. By means of subsequent functional analyses and literature search, as well as additional integrative analyses, we identified the 20 top priority candidate genes: *ALDH2*, *APOE*, *CAPZA1*, *CYP11B2*, *GNA13*, *IL6*, *IRF5*, *LDLR*, *LPL*, *LSP1*, *MKNK1*, *MMP3*, *MTHFR*, *MYO6*, *NCR3*, *PPARG*, *SARM1*, *TCF20*, *TCF7L2*, and *TNF*. Interrogation of the Variation Viewer and PharmGKB databases identified variants with the highest frequencies and those with pharmacological relevance in the human population. These genes provide important leads to design future nutrigenetic studies for the development of precise nutrition.

Keywords: interindividual variability; genetic polymorphisms; hypertension; atherosclerosis; arterial stiffness; cardiovascular; nutrigenomics; nutrigenetics

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