Arachidonate 5-Lipoxygenase Variants in Atherosclerosis, Obesity, and Bone Traits

To the Editor:

I write regarding publications by Mehrabian et al.1–2 appearing in Circulation Research and a subsequent publication by Kuhn et al3 appearing in Arteriosclerosis, Thrombosis, and Vascular Biology. The key implication from the combination of these reports was that amino acid substitutions in arachidonate 5-lipoxygenase (ALOX5) could account for differences in susceptibility to atherosclerosis between mouse strains CAST/EiJ and C57BL/6J. The two putative amino acid substitutions reported by Mehrabian et al to be present in strain CAST/EiJ1 were at positions 645 and 646, which are conserved across human, mouse, rat, dog, cow, and chicken. Indeed, when Kuhn et al4 mutated either or both of these residues in the human cDNA, ALOX5 activity was markedly impaired suggesting a key role for one or both of these residues in protein function. Recently, I determined that the coding sequences reported in the first article and implemented in the third article are incorrect.

We detected QTLs for cholesterol traits on Chr 6 in crosses between strains CAST/EiJ and 129S1/SvImJ5 and between strains CAST/EiJ and DBA/2J6,7 that colocalized with Alox5. The coding region of Alox5 was sequenced among these inbred mouse strains. On comparison of all sequences, we made four observations. (1) Our deduced amino acid sequence derived from strain CAST/EiJ (genomic DNA and cDNA) was different to that reported by Mehrabian et al.1 (2) The amino acid sequence for strain CAST/EiJ was identical to strain C57BL/6J. (3) Residue 645 was identical among all the mouse strains. (4) Strains 129S1/SvImJ and DBA/2J exhibited ALOX5 amino acid identity, but differed from strains among all the mouse strains. (4) Strains 129S1/SvImJ and DBA/2J5,6 that colocalized with D6Mit102-D6Mit198 (C57BL/6J versus CAST/EiJ) and from altered transcriptional or translational efficiency (C57BL/6J versus DBA/2J). This highlights the appearance in different ancestral populations (eg, Mus musculus, M. m. domesticus, M. m. castaneus) of alternative variants that arise within a single gene that act via different modes of activity, but exhibit similar phenotypic results. Furthermore, these observations demonstrate the ability of QTL mapping approaches to detect both types of genetic variation when they occur within genes whose products are key regulators of biological processes.

Malcolm A. Lyons
Western Australian Institute for Medical Research and Centre for Medical Research
University of Western Australia
Perth, Australia


Arachidonate 5-Lipoxygenase Variants in Atherosclerosis, Obesity, and Bone Traits
Malcolm A. Lyons

Circ Res. 2006;98:e66
doi: 10.1161/01.RES.0000219674.81938.63

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/98/8/e66

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/