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Are IA-2 and RESP18 Involved in Trait of Blood Pressure?

To the Editor:

Congenic rat strains are important tools for the genetic dissection of essential hypertension.1 Garrett et al recently demonstrated that a blood pressure (BP) quantitative trait locus (QTL) exists within a newly defined 117-kb QTL region on rat chromosome 9.2 By using microarray technology, the authors first found that the mRNA of Resp18 (endocrine-specific protein 18) is ~7.27-fold lower in the kidney of S.R(9)x3A congenic rats (Dahl salt-resistant) than that of S rats (Dahl salt-sensitive). Furthermore, sequencing analysis revealed multiple mutations of Resp18, particularly the sequence variation (T/C) in exon 2. However, a fine-map analysis showed that Resp18 is located just outside of the 117-kb QTL region; thus, Resp18 was eliminated as a candidate gene.

The authors, however, did not address: (1) whether a homolog gene of Resp18 exists in genome, particularly in the 117-kb QTL region; (2) the significance of the Resp18 sequence variation (T/C) in exon 2; and (3) the possibilities that RESP18 plays a role in BP.

We recently demonstrated that RESP18 not only shares significant sequence similarities with the N-terminal domain (amino acid 1–200) of IA-2, a dense-core vesicle (DCV)-transmembrane protein, but also shows a similar biological function to IA-2 in terms of exocytosis of neuronal transmitter and hormones.3,4 This means we have demonstrated that RESP18, as a DCV cargo protein, is also involved in DCV secretion (P. Yu et al, unpublished data, 2005). Furthermore, our bioinformatic analysis showed that Resp18 shares similar genomic structure and is tandemly arranged with IA-2 within a small genomic region. In rat, Resp18 is located ~9 kb of the 5’ terminus of IA-2 (GenBank accession number AC121633), indicating that IA-2 is within the 117-kb QTL region.

We found that the sequence variation (T/C) in exon 2 (nt 272) of Resp18 actually results in a Ile/Pro (aa 62) change in the predicted protein product rather than a Ile/Val as reported. This variation (T/C) is not found in >100 expressed sequence tags of rat Resp18 (http://www.ncbi.nlm.nih.gov/BEAST/), suggesting it is a rare polymorphism or a mutation. Furthermore, our evolutionary analysis revealed that substitution of Ile/Pro is not present in all species we examined, whereas Ile and Val are present in these species (see below, bold in multiple sequences alignment). But the effects of the Ile/Pro change on DCV secretion of RESP18 need to be examined.

Mouse RESP18 57 FGYLQLIFHQIVPQGMF. Rat RESP18 57 FQYLQLFHHHVQPGMF. Bovine RESP18 57 FQHLQQVLQHIVPQGLF. Pig Resp18 57 FQHLQWLQIVVPQGLF. Human RESP18a57 FQHLQQVLQHIVPQGLF.

A recent in vivo evidence demonstrated that DCV formation and activity, which is regulated by chromogranin, is tightly coupled to the action of catecholamine and BP regulation.5 We speculated that IA-2 probably is the causative gene for the 117-kb BP QTL, and RESP18 might also possess an additive effect on the BP by regulating DCV cargo release or other mechanisms. To test this hypothesis, our experiments by using IA-2 deficient mice are underway.

Tao Cai
Experimental Medicine Section, Oral Infection and Immunity Branch
National Institute of Dental and Craniofacial Research/National Institutes of Health
Bethesda, Maryland

References

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Tao Cai

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