**Response**

The fundamental premise of substitution mapping is to be able to track the blood pressure (BP) effects of quantitative trait loci (QTL) that are introgressed within a congenic strain. Based on this paradigm, our report\(^1\) clearly excludes *Resp18* as the QTL within the 117-kb region of interest. Cai contemplates the possibility that *Resp18* plays a role in BP. In our opinion, a good experiment to test this is to study a minimal congenic strain around the *Resp18* locus.

Cai brings out an interesting point of whether a homolog of *Resp18* exists in the critical 117-kb region. *IA-2*, or *ICA512*, is one such gene, the protein product of which was originally reported to have 27% identity and 56% similarity with the 18-kDa *Resp18* protein.\(^2\) We are glad that Cai could utilize the data presented in our manuscript and arrive at 2 speculations: (1) *IA-2* is probably the causative gene for the 117-kb BP QTL. The least that this speculation could be based on is a single nucleotide polymorphism (SNP) of *IA-2* between Dahl salt-sensitive (S) rats and Dahl salt-resistant (R) rats. We have identified numerous SNPs between the S and R rat within and around *IA-2*. Unpublished data demonstrate that, at least independently, none of these SNPs affect BP. Further, the microarray experiment reported in our article\(^1\) did not detect any renal differential expression of *IA-2* between S and the congenic strain (GEO accession no. GSE 1775, probes D38222_s_at and rc_AI137484_at). Thus, so far we do not have any evidence, at the level of either the gene sequence or transcription, to suggest that *IA-2* is the BP QTL. Cai indicates that experiments using mouse *IA-2* are underway. We look forward to the results of this study. Nevertheless, phenotypic effects of knockout mice may not always reflect the properties of natural allelic variants of a gene in a congenic strain.\(^3,4\) (2) *Resp18* and *IA-2* may possess an additive effect on BP. This speculation is contrary to the data provided in our report,\(^1\) wherein we have demonstrated that the effects of the QTL gene within the 117-kb region and that of *Resp18* are not additive.\(^5\)

The amino acid substitution of *Resp18* is correct in our report (ie, the sequence variation is from Isoleucine [Ile] to Valine [Val]). However, there is a discrepancy in the location of nucleotide coding for this amino acid substitution. The T/C variation reported in Figure 3 of our article\(^1\) is that of genomic DNA. This variation corresponds to a SNP of A/G at position 286 (not 272 as reported) from the 5’ untranslated region of the mRNA transcript of *Resp18*. This SNP alters the amino acid 67 of *Resp18* from Ile in S rats to Val in R rats.

Finally, please note that in Cai’s letter there is some confusion about amino acid 62. It is referred to as Ile (Isoleucine) in the text, but depicted as L (Leucine) within the sequence comparisons. We would like to clarify that amino acid 62 is L in the protein database (NP_062151 at http://www.ncbi.nlm.nih.gov) as well as in S and R rats.

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