Human Nedd4L rs4149601 G Allele Generates Evolutionary New Isoform I With C2 Domain

To the Editor:

We carefully read the recent article in Hypertension by Luo et al.1 They found that the human Nedd4L functional variant (rs4149601 [G/A]) shows significant functional relevance with various phenotypes of human hypertension. However, they repeatedly emphasized in the article that, “the cryptic splice variant rs4149601 (G/A) A allele of NEDD4L, generating isoform I” was estimated to be associated with those functional phenotypes. We need to address one important issue they must consider. Because isoform I of human Nedd4L was generated by a G allele of NEDD4L with an evolutionary new C2 domain,2 the discussion and interpretation in their article should be reconsidered in accordance with this point. As we reported previously, products of the Nedd4L gene for both humans and rodents showed molecular diversity.2,3 Among them, the human Nedd4L gene was more complicated because the G allele of rs4149601 generated an evolutionary new isoform with the C2 domain called “isoform I.” On the other hand, the A allele of rs4149601 failed to be spliced appropriately and resulted in a stop codon in exon 2.2 Therefore, the subjects with the A allele have no isoform I. A previous report also showed that the subjects with a G allele showed significant associations for hypertension and its related phenotype.4 In addition, in in vitro electrophysiological functional assay using Xenopus oocyte heterologous gene expression systems, we reported that isoform I would suppress ubiquitination for cell surface ENaC by 2 other isoforms.5

Disclosures

None.

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