Supplemental Material

Figure S1

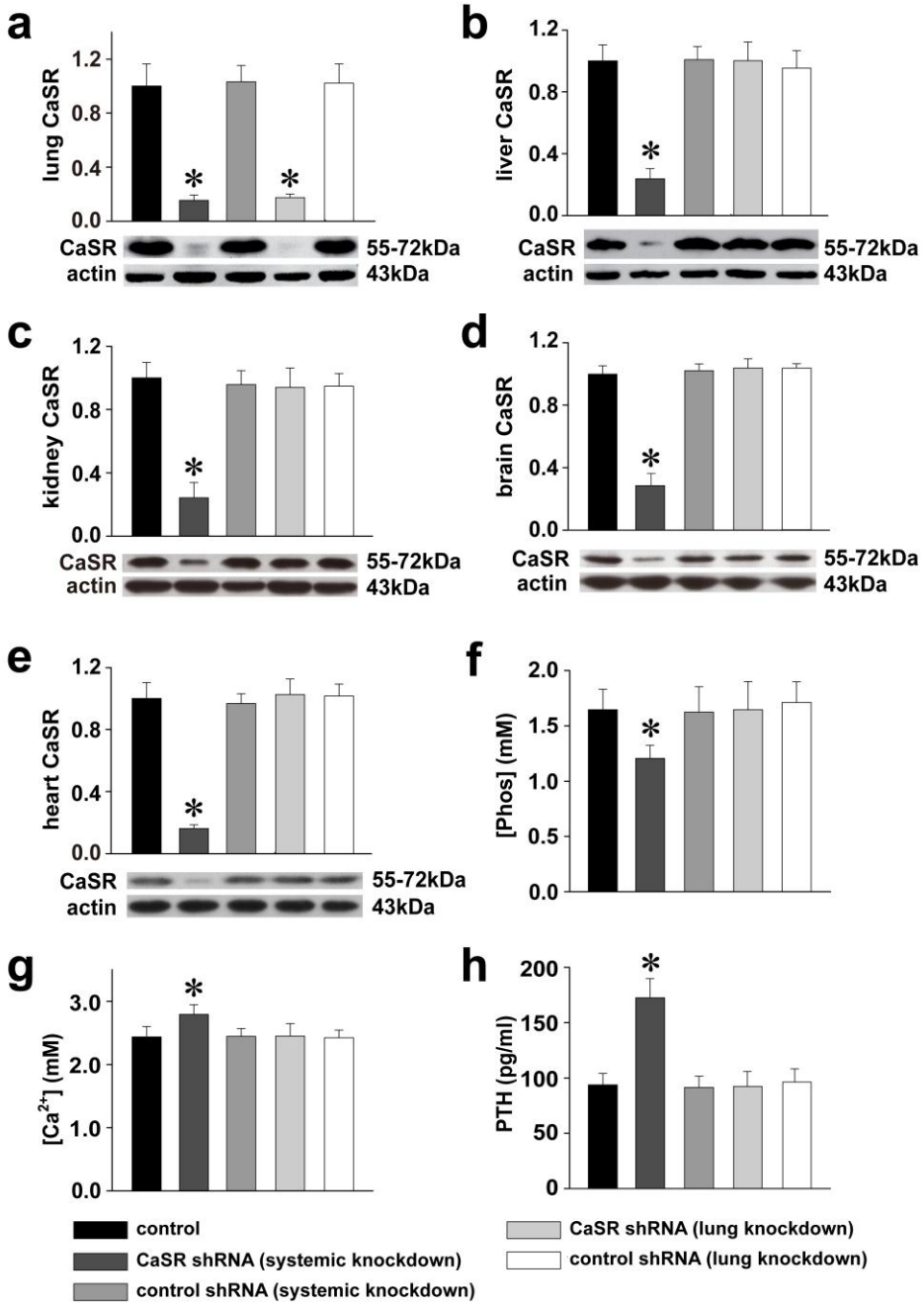

Figure S1 **The systemic and lung knockdown of extracellular calcium-sensing receptor.**

Representative immunoblots and statistical summaries of extracellular calcium-sensing receptor (CaSR) expression levels in organs of lung (**a**), liver (**b**), kidney (**c**), brain (**d**) and heart (**e**) as well as serum levels of phosphate (**f**), calcium (**g**) and parathyroid hormone (PTH, **h**) in blank control rats, rats intravenously or intratracheally transduced with CaSR shRNA or control shRNA for systemic and lung CaSR knockdown, respectively. * $p < 0.05$ vs. control, n=3 for each group.

Figure S2

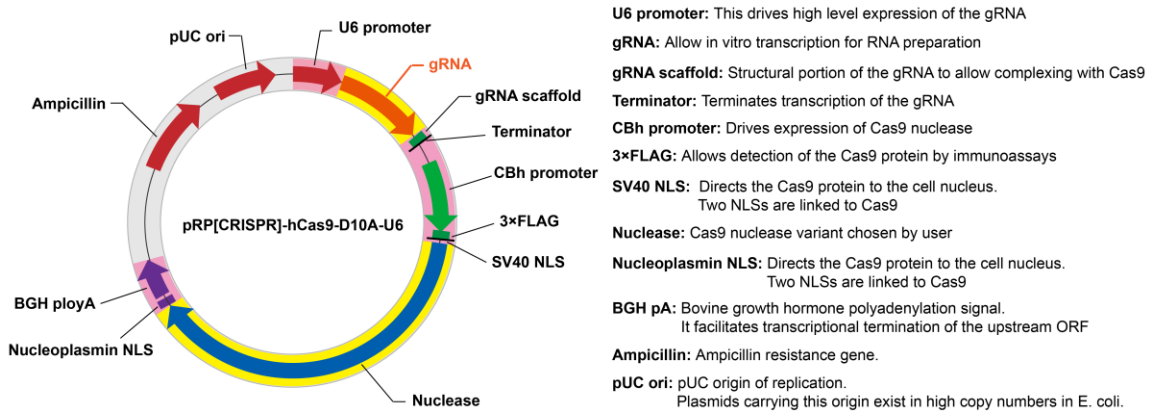

Figure S2 The map of pRP[CRISPR]-hCas9_D10A-U6 vector.

Figure S3

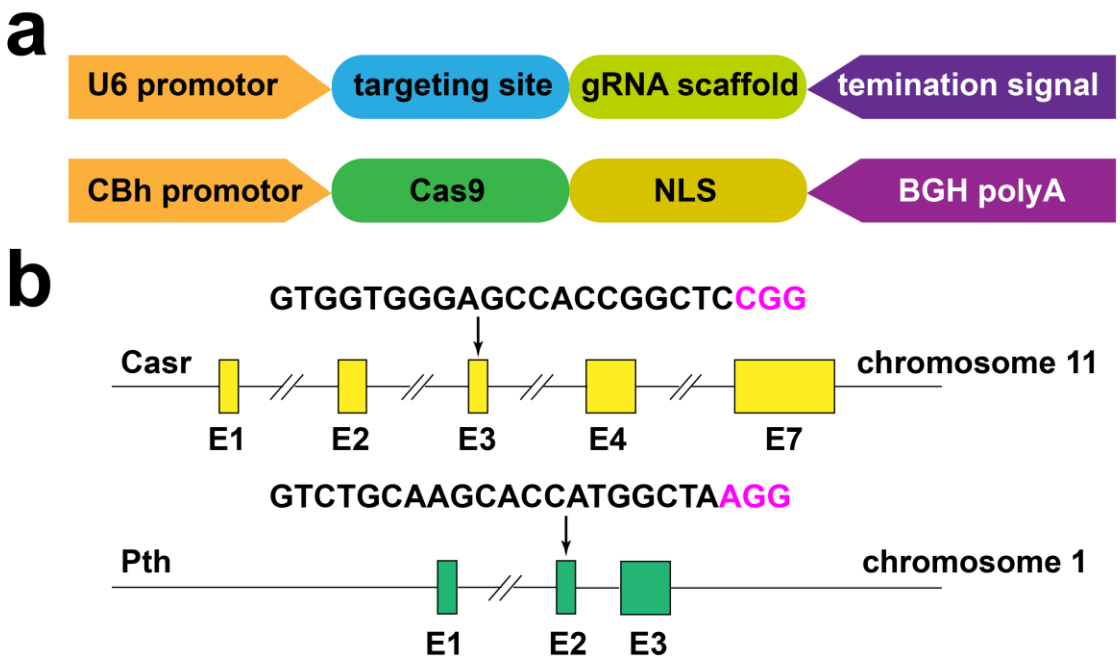

Figure S3 Genome editing via Cas9/gRNA system in SD rats.

a. Constructs and schematic illustration of the Cas9/gRNA system used in this experiment. The U6 promoter drives transcription of the gRNA, which consists of a target sequence and a scaffold sequence. CBh promoter: drives the expression of Cas9 nuclease. NLS: nuclear localization signal. BGH polyA: bovine growth hormone polyadenylation signal, it facilitates transcriptional termination of the upstream ORF.

b, Target sequence of extracellular calcium-sensing receptor (Casr) and parathyroid hormone (Pth). The rCasr gene is located on chromosome 11 and seven exons have been identified. Exon 3 (E3) was selected as Cas9 targeting regions and gRNA targeting sequences were labeled above in the E3. The rPth gene is located on chromosome 1 and three exons have been identified. E2 was selected as Cas9 targeting regions and gRNA targeting sequences were labeled above in the E2. PAM (protospacer adjacent motif, which is indispensable for Cas9 binding and cleavage) sequences are highlighted in pink.

Figure S4

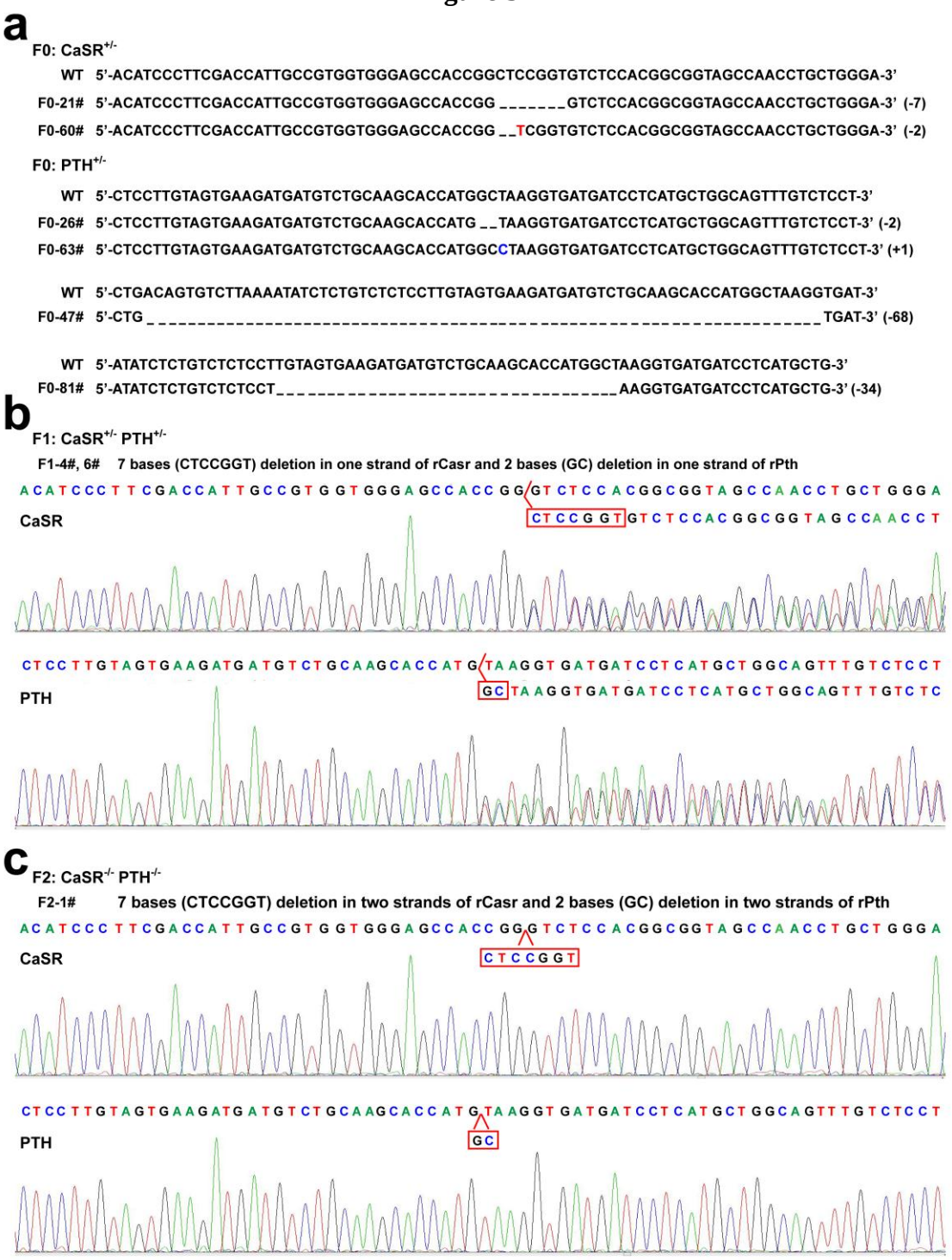

Figure S4 Generation of extracellular calcium-sensing receptor (CaSR) and parathyroid hormone (PTH) double knockout rats.

a. Detailed mutations of CaSR and PTH gene in F0 knockout (KO) rats. Deletions are indicated by dashes, insertions are indicated in blue and substitutions are indicated in red. Deletions (-) and insertions (+) are shown to the right of each allele. **b**. Detailed mutations of CaSR and PTH gene in F1 KO rats. **c**. Detailed mutations of CaSR and PTH gene in F2 KO rats.