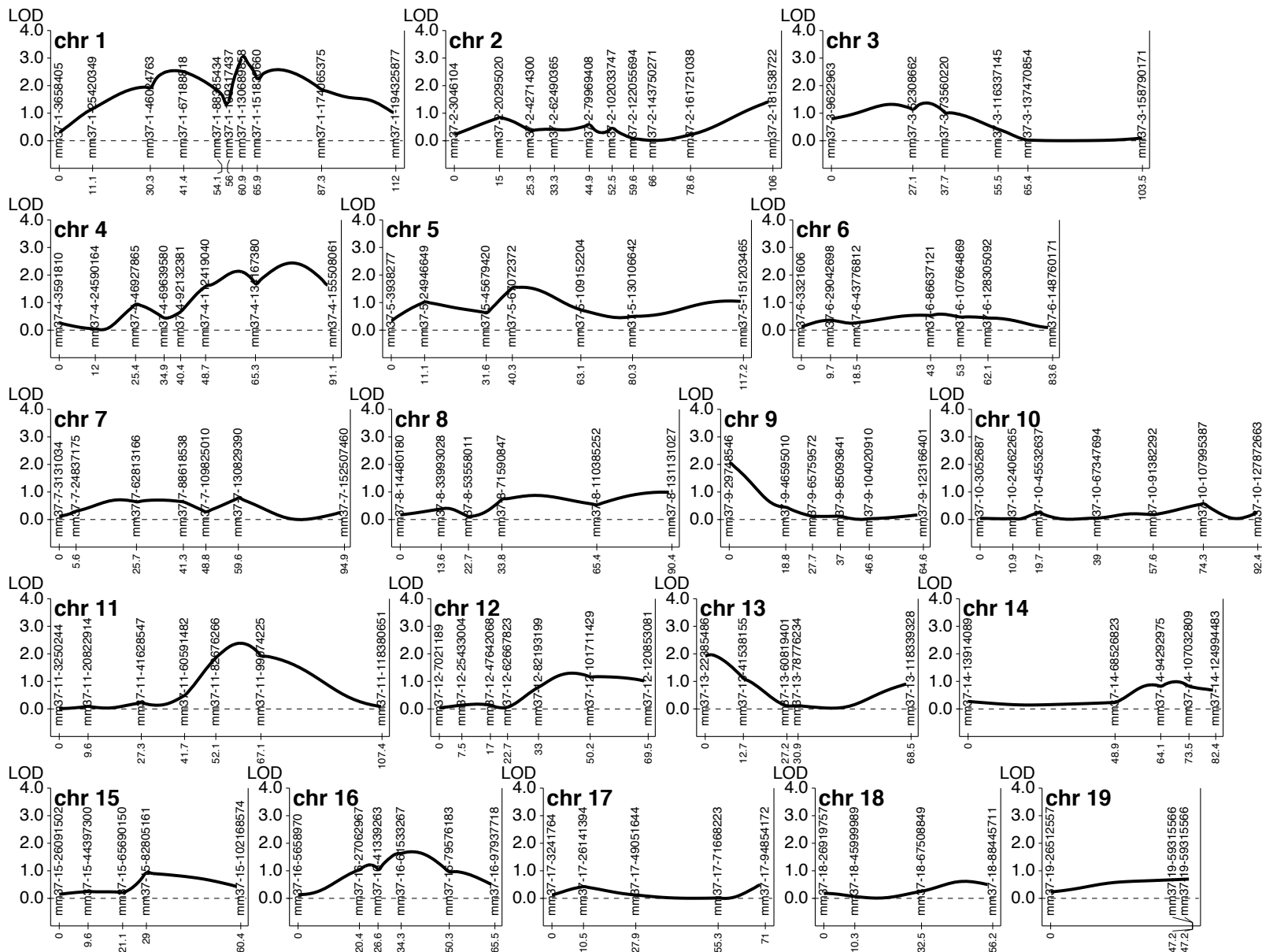
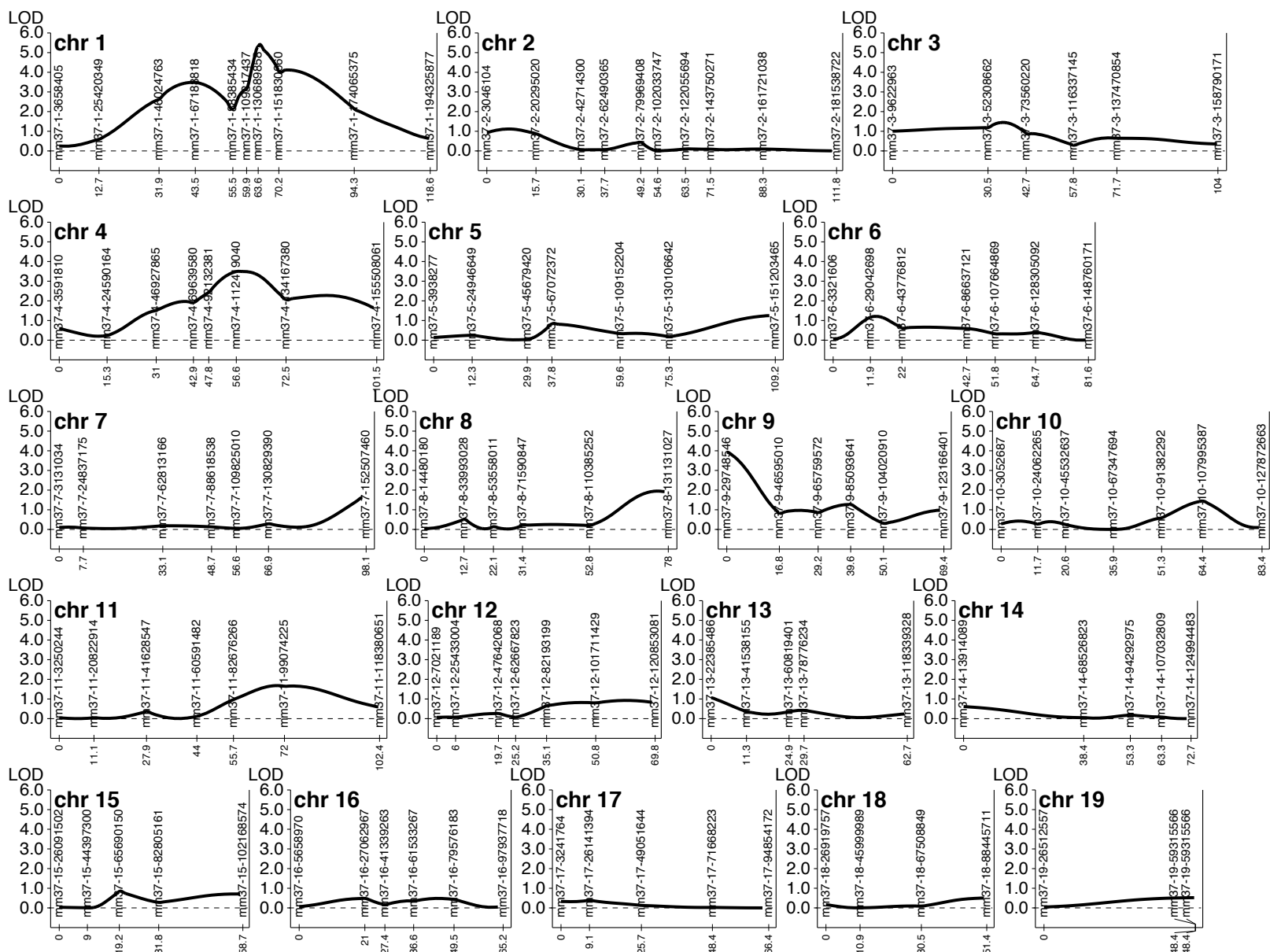


Supplemental Figure 1. Genome-wide linkage scan, using 120 single nucleotide polymorphism (SNP) markers, for blood pressure in 92 male $sGC\alpha_1^{-/F2}$ ($sGC\alpha_1^{-/S6}$ X $sGC\alpha_1^{-/B6}$) progeny. Separate plots were generated for chromosome (chr) 1 through 19 with the SNP markers used to genotype the mice plotted on the X-axis. The Y-axis represents the LOD scores. One locus (on chromosome 1) showed suggestive linkage to blood pressure.



Supplemental Figure 2. Genome-wide linkage scan, using 120 single nucleotide polymorphism (SNP) markers, for blood pressure in a separate cohort of 96 male $sGC\alpha_1^{-/F2}$ ($sGC\alpha_1^{-/S6}$ X $sGC\alpha_1^{-/B6}$) progeny. Separate plots were generated for chromosome (chr) 1 through 19 with the SNP markers used to genotype the mice plotted on the X-axis. The Y-axis represents the LOD scores. One locus (on chromosome 1) showed suggestive linkage to blood pressure.



Supplemental Figure 3. Genome-wide linkage scan, using 120 single nucleotide polymorphism (SNP) markers, for blood pressure in 188 male $sGC\alpha_1^{-/F2}$ ($sGC\alpha_1^{-/S6}$ X $sGC\alpha_1^{-/B6}$) progeny (the combined linkage analysis of all 92 and 96 $sGC\alpha_1^{-/F2}$ mice in supplemental figures 1 and 2, respectively). Separate plots were generated for chromosome (chr) 1 through 19 with the SNP markers used to genotype the mice plotted on the X-axis. The Y-axis represents the LOD scores. One locus (on chromosome 1) showed significant linkage to blood pressure. Two loci (on chromosomes 4 and 9) showed suggestive linkage to blood pressure (LODs of 3.6 and 3.9, respectively).

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-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      10      20      30      40      50      60      70      80      90      100     110     120     130     140     150
1 GGAGTCTGGACAGCCTACATGACTGATGGCCACAGAATTATGGAGCTGGGTCTTGGCCAGAAAAACAGGCTGCCTTTCATGGTCCCACAGGCCCTGGGGTAATAAATCAAAGCAGAGCCTGTGATACATGGTGTGTATAAAAAGAGGCTC Renin-1c
1 GGAGTCTGGACAGCCTACATGACTGATGGCCACAGAATTATGGAGCTGGGTCTTGGCCAGAAAAACAGGCTGCCTTTCATGGTCCCACAGGCCCTGGGGTAATAAATCAAAGCAGAGTCTGTGATACATGGTGTGTATAAAAAGAGGCTC Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      160     170     180     190     200     210     220     230     240     250     260     270     280     290     300
151 AGGGGGTCTGGGCTACACAGCTCTTAGAAAGCCTTGGCTGAACCAGATGGACAGAGAGGAGGATGCCTCTCTGGGCACTCTTGTGCTCTGGAGTCCCTTGCACCTTCAGTCTCCCAACACGCACCCGCTACCTTTGAACGAATCCCCTCAA Renin-1c
151 AGGGGGTCTGGGCTACACAGCTCTTAGAAAGCCTTGGCTGAACCAGATGGACAGAGAGGAGGATGCCTCTCTGGGCACTCTTGTGCTCTGGAGTCCCTTGCACCTTCAGTCTCCCAACACGCACCCGCTACCTTTGAACGAATCCCCTCAA Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      310     320     330     340     350     360     370     380     390     400     410     420     430     440     450
301 GAAAAATGCCCTCTGTCGGGAAATCCTGGAGGAGCGGGGAGTGGACATGACCAGGCTCAGTGTCTGAAAGGGGCGTATTACAAAAGAGGCCCTCCTTGAACAATCTTACCTCCCCGCTGGTCTCACCAACTACCTGAATACCCAGTACTA Renin-1c
301 GAAAAATGCCCTCTGTCGGGAAATCCTGGAGGAGCGGGGAGTGGACATGACCAGGCTCAGTGTCTGAAAGGGGCGTATTACAAAAGAGGCCCTCCTTGAACAATCTTACCTCCCCGCTGGTCTCACCAACTACCTGAATACCCAGTACTA Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      460     470     480     490     500     510     520     530     540     550     560     570     580     590     600
451 CGGCGAGATTGGCATCGGTACCCACCCAGACCTTCAAAGTCATCTTTGACACGGGTTCCGCCAACCTCTGGGTGCCCTCCACCAAGTGCAGCCGCCTACCTTGCTGTGGGATTACAGCCTCTATGAGTCTCTGACTCCTCCAG Renin-1c
451 CGGCGAGATTGGCATCGGTACCCACCCAGACCTTCAAAGTCATCTTTGACACGGGTTCCGCCAACCTCTGGGTGCCCTCCACCAAGTGCAGCCGCCTACCTTGCTGTGGGATTACAGCCTCTATGAGTCTCTGACTCCTCCAG Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      610     620     630     640     650     660     670     680     690     700     710     720     730     740     750
601 CTACATGGAGAACGGGTCGACTTCACCATCCACTACGGATCAGGAGAGTCAAAGGTTTCCTCAGCCAGGACTCGGTGACTGTGGTGGGAATCACTGTGACACAGACCTTTGGAGAGGTACCCAGCTGCCCTGATCCCTTTCATGCT Renin-1c
601 CTACATGGAGAACGGGTCGACTTCACCATCCACTACGGATCAGGAGAGTCAAAGGTTTCCTCAGCCAGGACTCGGTGACTGTGGTGGGAATCACTGTGACACAGACCTTTGGAGAGGTACCCAGCTGCCCTGATCCCTTTCATGCT Renin-1d
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      760     770     780     790     800     810     820     830     840     850     860     870     880     890     900
751 GGCCAAGTTTGACGGTGTCTAGGCATGGGCTTTCCTGCTCAGGCCGTTGGCGGGTTACCCCTGTCTTTGACCACATTCTCTCCAGGGGGTGTAAAGGAGGAAGTGTCTCTGTCTACTACAACAGGGGTTCCCACTGTGGGGG Renin-1c
751 GGCCAAGTTTGACGGTGTCTAGGCATGGGCTTTCCTGCTCAGGCCGTTGGCGGGTTACCCCTGTCTTTGACCACATTCTCTCCAGGGGGTGTAAAGGAGGAAGTGTCTCTGTCTACTACAACAGGGGTTCCCACTGTGGGGG Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      910     920     930     940     950     960     970     980     990     1000    1010    1020    1030    1040    1050
901 CGAGGTGGTGTAGGAGTACCGACCCGACATTACCAAGCAATTTACTATGTGAGCATCAGCAAGACTGACTCCTGGCAGATCAGCATGAAGGGGGTGTCTGTGGGGTCTTCCACCTGCTATGTGAAGAAGGCTGTGCGGTAGT Renin-1c
901 CGAGGTGGTGTAGGAGTACCGACCCGACATTACCAAGCAATTTACTATGTGAGCATCAGCAAGACTGACTCCTGGCAGATCAGCATGAAGGGGGTGTCTGTGGGGTCTTCCACCTGCTATGTGAAGAAGGCTGTGCGGTAGT Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      1060    1070    1080    1090    1100    1110    1120    1130    1140    1150    1160    1170    1180    1190    1200
1051 GGTGGACACTGGTTCATCTTTATCTCGGCTCCTACGAGCTCCCTGAAGTTGATCATGCAAGCCCTGGGAGCCAAGGAGAAGAGAATAGAGAATATGTTGTGAAGTGTAGCCAGGTGCCACCTCCCGACATTTCCCTTTGACCTGGG Renin-1c
1051 GGTGGACACTGGTTCATCTTTATCTCGGCTCCTACGAGCTCCCTGAAGTTGATCATGCAAGCCCTGGGAGCCAAGGAGAAGAGAATAGATGAATATGTTGTGAAGTGTAGCCAGGTGCCACCTCCCGACATTTCCCTTTGACCTGGG Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      1210    1220    1230    1240    1250    1260    1270    1280    1290    1300    1310    1320    1330    1340    1350
1201 AGGCAGGGCCTACACACTCAGCAGTACGGACTACGTGCTACAGTATCCCAACAGGAGAGACAAGCTGTGCACACTGGCTCTCCATGCCATGGACATCCCACCACCACCTGGGCTGTCTGGGTCTGGTGGCCACCTTCATCCGCAAGTT Renin-1c
1201 AGGCAGGGCCTACACACTCAGCAGTACGGACTACGTGCTACAGTATCCCAACAGGAGAGACAAGCTGTGCACACTGGCTCTCCATGCCATGGACATCCCACCACCACCTGGGCTGTCTGGGTCTGGTGGCCACCTTCATCCGCAAGTT Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      1360    1370    1380    1390    1400    1410    1420    1430    1440    1450    1460    1470    1480    1490    1500
1351 CTATACAGAGTTTGATCGGCATAAACAATCGCATTGGATTTCGCCTTGGCCCGCTAAGGCCCTCTGCCACCAGTAACCTTAGGCCAAGCCAAGCTGGCACTCCTGGGGCCATTTTGTCTGGCTTTGTCCCAACATAGGGACTGGACA Renin-1c
1351 CTATACAGAGTTTGATCGGCATAAACAATCGCATTGGATTTCGCCTTGGCCCGCTAAGGCCCTCTGCCACCAGTAACCTTAGGCCAAGCCAAGCTGGCACTCCTGGGGCCATTTTGTCTGGCTTTGTCCCAACATAGGGACTGGACA Renin-1d
-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      1510    1520    1530    1540    1550    1560    1570    1580    1590
1501 CAGAGACCCTAACGAGTGTTCGCCCTTACCTGCACCTACCTTCCCTGCTTTAAGGAAAAATCGAATAAAGATTTCATGTTTAAAGCCTG Renin-1c
1501 CAGAGACCCTAACGAGTGTTCGCCCTTACCTGCACCTACCTTCCCTGCTTTAAGGAAAAACCGAATAAAGATTTCATGTTTAAAGCCTG Renin-1d

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Supplemental Figure 4. Alignment of the cDNA sequences of renin1-d (the S6 allele, upper strand) and renin1-c (the B6 allele, lower strand). The 21 residues that differ between the 2 strains are highlighted in yellow.

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-----+-----+-----+-----+-----+-----+-----+-----+-----+
      10      20      30      40      50      60      70      80      90     100
1  MDRRRMPLWALLLLWSPCTFSLPTRTATFERIPLKKMPSVREILEERGVDMTRLSAEWGVFTKRPSLTINLTSPVVLTNYLNTQYYGEIGIGTPPQTFKVI Renin-1c
1  MDRRRMPLWALLLLWSPCTFSLPTRTATFERIPLKKMPSVREILEERGVDMTRLSAERGVFTKRPSLTINLTSPVVLTNYLNTQYYGEIGIGTPPQTFKVI Renin-1d

-----+-----+-----+-----+-----+-----+-----+-----+-----+
      110     120     130     140     150     160     170     180     190     200
101 FDTGSANLWVPSTKCSRLLYLACGIHSLYESSDSSSYMENGSDFTIHYGSGRVKGFSLQDSVTVGGITVTQTTFGEVTELEPLIPFMLAKFDGVLGMGFPAQA Renin-1c
101 FDTGSANLWVPSTKCSRLLYLACGIHSLYESSDSSSYMENGSDFTIHYGSGRVKGFSLQDVTTVGGITVTQTTFGEVTELEPLIPFMLAKFDGVLGMGFPAQA Renin-1d

-----+-----+-----+-----+-----+-----+-----+-----+-----+
      210     220     230     240     250     260     270     280     290     300
201 VGGVTPVFDHILSQVGLKEEVFSVYYNRGSHLLGGEVVLGGSDPQHYQGNFHYVVISKTDQITMKGVSVGSSTLLCEECAVVVDTGSSSFISAPTSSL Renin-1c
201 VGGVTPVFDHILSQVGLKEEVFSVYYNRGSHLLGGEVVLGGSDPQHYQGNFHYVVISKTDQITMKGVSVGSSTLLCEECAVVVDTGSSSFISAPTSSL Renin-1d

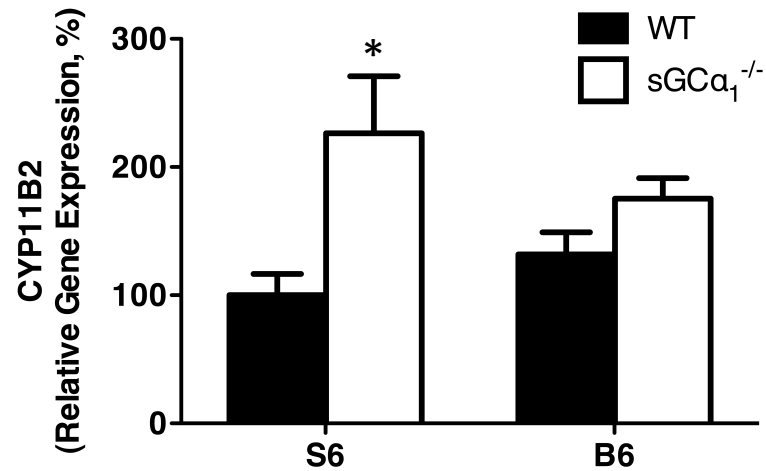
-----+-----+-----+-----+-----+-----+-----+-----+-----+
      310     320     330     340     350     360     370     380     390     400
301 KLIMQALGAKEKRIEYVNVNCSQVPTLPDISFDLGGRAYTLSSDYVLQYFNRRDKLCTLALHAMDIPPTGPVWVLGATFIRKFYTEFDRHNNRIGFAL Renin-1c
301 KLIMQALGAKEKRIDEYVNVNCSQVPTLPDISFDLGGRAYTLSSDYVLQYFYRRDKLCTLALHAMDIPPTGPVWVLGATFIRKFYTEFDRHNNRIGFAL Renin-1d

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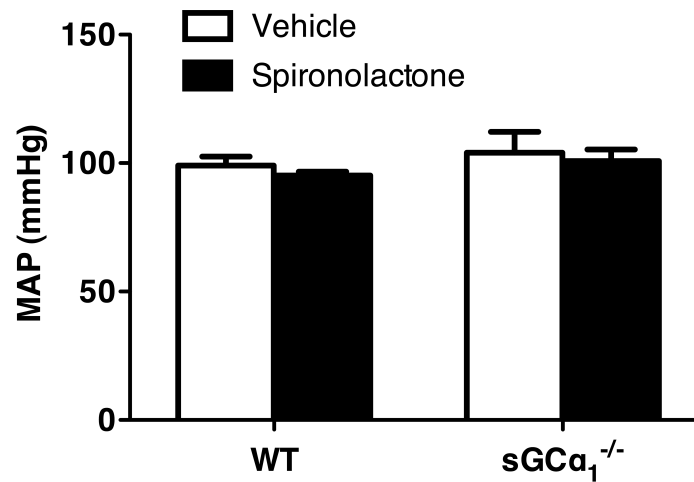
401 AR Renin-1c
401 AR Renin-1d

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Supplemental Figure 5. Alignment of the amino acid sequences of renin1-d (the S6 allele, upper strand) and renin1-c (the B6 allele, lower strand). The 5 amino acids that differ between the 2 strains are highlighted in yellow.

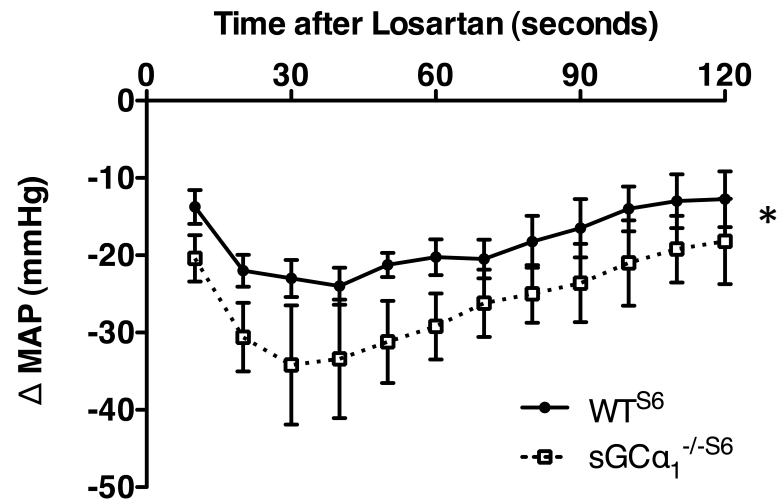


Supplemental Figure 6. Adrenal CYP11B2 expression is higher in sGC $\alpha_1^{-/-S6}$ than in WT^{S6} mice . mRNAs encoding the cytochrome P450, family 11, subfamily b, polypeptide 2 (CYP11B2 or aldosterone synthase) were measured via quantitative RT-PCR in adrenal glands of male WT and sGC $\alpha_1^{-/-}$ mice on the S6 or B6 genetic background. N=8-11/group. Adrenal expression level of CYP11B2 was higher in sGC $\alpha_1^{-/-S6}$ than in WT^{S6} mice. *P<0.01 vs WT^{S6}.

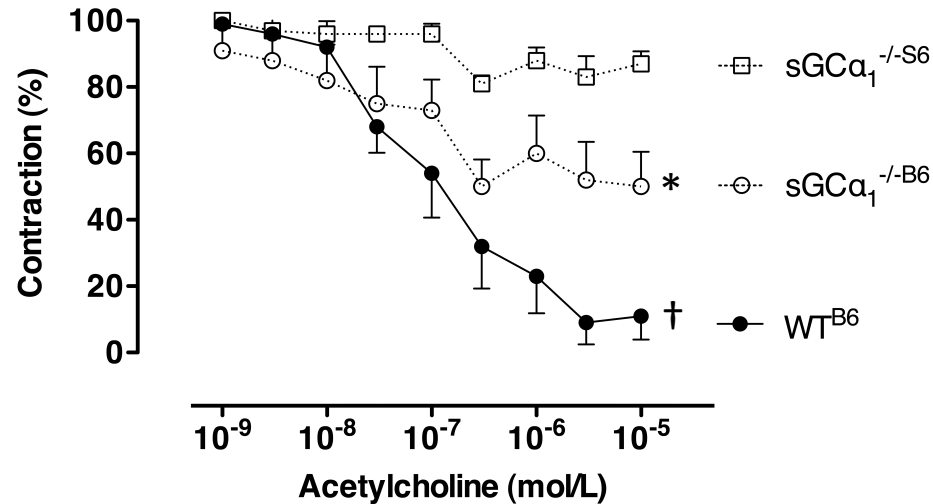


Supplemental Figure 7. Spironolactone does not affect blood pressure in WT^{B6} or sGC $\alpha_1^{-/-}$ B6 mice.

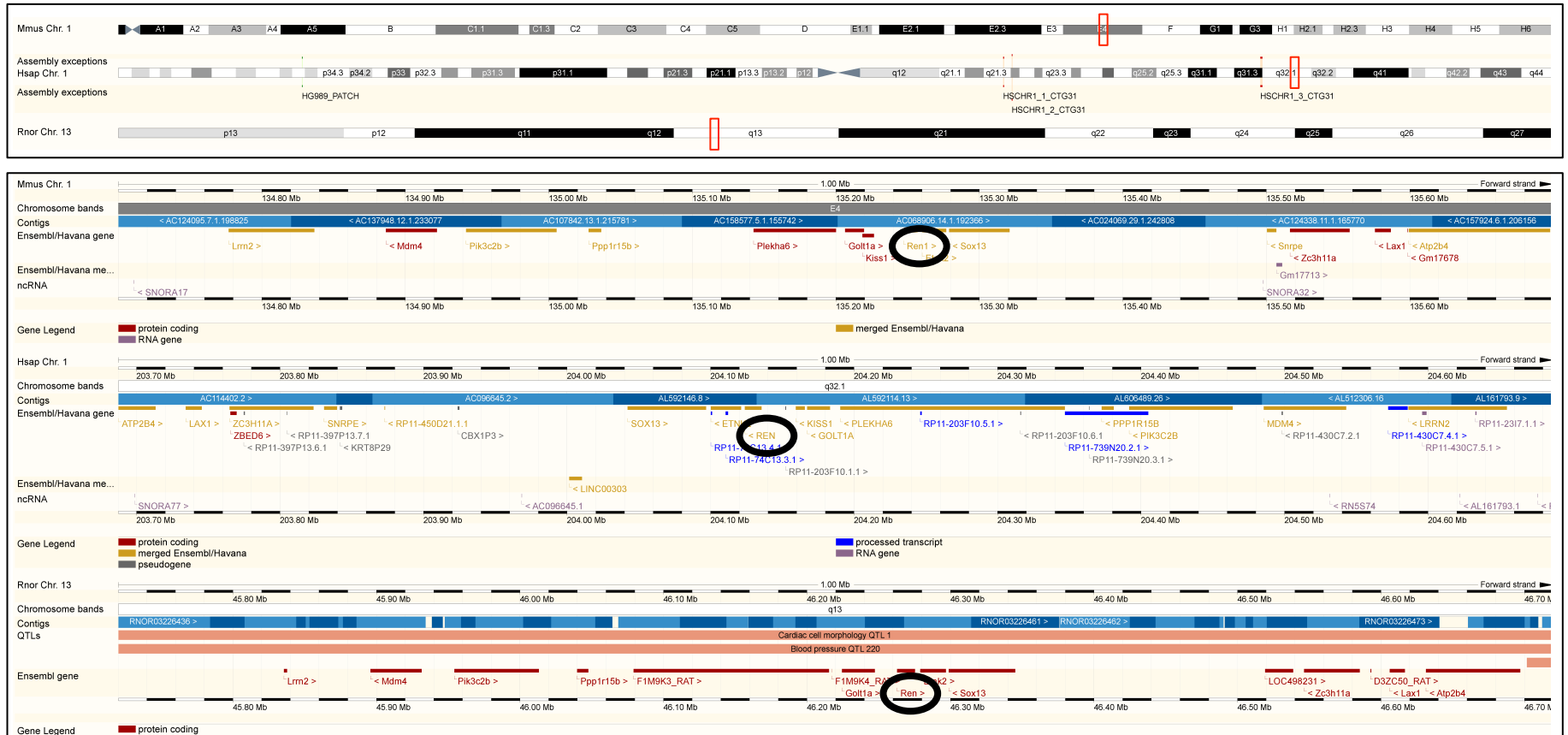
Mean arterial blood pressure (MAP) measured invasively in anesthetized male WT and sGC $\alpha_1^{-/-}$ mice on the B6 background, treated with vehicle (n=5 and 3, respectively) or spironolactone (n=5 and 6, respectively). P=NS for WT vehicle vs WT Spironolactone and for sGC $\alpha_1^{-/-}$ vehicle vs sGC $\alpha_1^{-/-}$ spironolactone (*t* test).



Supplemental Figure 8. Losartan decreases blood pressure more in sGCα₁^{-/-S6} mice than in WT^{S6} mice. Decrease in mean arterial blood pressure (MAP) measured invasively in anesthetized male WT and sGCα₁^{-/-} mice on the S6 background, treated intravenously with 0.1 mg/kg Losartan (n=4 and 5, respectively). Repeated measures Anova *P< 0.001.



Supplemental Figure 9. The strain-specific hypertension in $sGC\alpha_1^{-/-}$ mice is associated with greater impairment of vascular reactivity in $sGC\alpha_1^{-/-S6}$ mice than in $sGC\alpha_1^{-/-B6}$ mice. Acetylcholine-induced relaxation was studied in phenylephrine-precontracted mesenteric arteries from male wild-type (WT, closed symbols, full line) and $sGC\alpha_1^{-/-}$ mice on the B6 (circles) or S6 (squares) genetic background. Acetylcholine-induced vascular relaxation was impaired to a greater extent in $sGC\alpha_1^{-/-S6}$ than in $sGC\alpha_1^{-/-B6}$ mice. N= 3, 5, and 6 for $sGC\alpha_1^{-/-S6}$, $sGC\alpha_1^{-/-B6}$, and WT^{B6}, respectively. *P<0.05 vs $sGC\alpha_1^{-/-S6}$, †P<0.05 vs $sGC\alpha_1^{-/-S6}$ and $sGC\alpha_1^{-/-B6}$.



Supplemental Figure 10. Schematic representation, generated via e!Ensembl of *Mus musculus* chromosome 1 (Mmus Chr.1), *Rattus norvegicus* chromosome 13 (Rnor Chr.13), and *Homo sapiens* chromosome 1 (Hsap Chr.1). The red boxes in the top panel represent part of the syntenic region containing the renin locus and are magnified in the multi-species view in the bottom panel. Black ovals highlight the location of the renin gene in the murine, human, and rat genome.

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-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      10      20      30      40      50      60      70      80      90     100
1 MD-RRRMLW-ALLLLWSPCTFSLPTRTATFERIPLKKMPSVREILEERGVDMLRLSAEWGVFTKRPSLINLTSPVVLNTNYLNTQYYGEIGIGTTPPQTFK Mouse Renin-1c
1 MDGWRMPRWGLLLLLLWGSCTFGLPTDTTTFKRIFLKRMPSTRESLKERGVDMARLGPEWSQPMKRLTLGNTTSSVILNTNYMDTQYYGEIGIGTTPPQTFK Human Renin

-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      110     120     130     140     150     160     170     180     190     200
99 VIFDTGSANLWVPSTKCSRLYLACGIHSLYESSDSSSYMENGSDFTTHYGSGRVKGFLSQDSVTGGITVTQTFGEVTELPLIPMLAKFDGVLGMGFPA Mouse Renin-1c
101 VVFDTGSSNVVWVPSSKCSRLYTACVYHKLFDASDSSSYKHNGTELTLYSTGTVSGFLSQDIITVGGITVTQMFGEVTEMLPPMLAEFDGVVGMGFIE Human Renin

-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      210     220     230     240     250     260     270     280     290     300
199 QAVGGVTPVFDHILSQGVLKEEVFSVYYNR---GSHLLGGEVVLGGSDPQHYQGNFHYVSISKTDSWQITMKGVSVGSSTLLCEEEGCAVVVDTGSSFISA Mouse Renin-1c
201 QAIGRVTPIFDNIISQGVLKEDVFSFYNRDSENSQSLGGQIVLGGSDPQHYEGNFHYINLIKTGVWQIQMKGVSVGSSTLLCEDGCLALVDTGASYISG Human Renin

-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+
      310     320     330     340     350     360     370     380     390     400
296 PTSSLKLIMQALGAKEKRIEEYVNCSQVPTLPDISFDLGGRAYTLSSTDYVLQYPNRRDKLCTLALHAMDIPPTGPVVWLGATFIRKFYTEFDRHNNR Mouse Renin-1c
301 STSSIEKLMEALGAK-KRLFDYVVKCNEGPTLPDISFHLGGKEYTLTSADYVFQESYSSKKLCTLALHAMDIPPTGPTWALGATFIRKFYTEFDRRNNR Human Renin

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396 IGFALAR Mouse Renin-1c
400 IGFALAR Human Renin

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Supplemental Figure 11. Alignment of the amino acid sequences of mouse renin1-c (the B6 allele, upper strand) and human renin-1 (lower strand). Amino acids that differ between murine renin1-c and human renin-1 are highlighted in yellow. The amino acids that differ between B6 and S6 (see **Supplemental Figure 5**) are highlighted in red.