Protein	pdb ID	Information
Prorenin	3vcm	Crystal structure of human renin (2.93 Å) with pro-domain added into renin
Prorenin	4amt	2.6 Å crystal structure for human prorenin
Angiotensinogen (AGT)	2wxw	Oxidized
	2wxx	Oxidized
	2wxy	Reduced
	2wxz	C2 space group
	2wy0	Oxidized in P6122 space group
	2wy1	P321 space group
Renin	1rne	Glycosylated and transition state analog inhibitor
	1bbs	Native
	2ren	Native
	1hrn	Polyhydroxymonoamide inhibitor
	1bil	Butanediamide inhibitor
	1bim	Butanediamide inhibitor
	2bks	PF00074777 COMPLEX
	2bkt	PF00257567 COMPLEX
	2fs4	Ketopiperazine-Based Inhibitor (PZ1)
	2g1n	Ketopiperazine-Based Inhibitor (1IG)
	2g1o	Ketopiperazine-Based Inhibitor (2IG)
	2g1r	Ketopiperazine-Based Inhibitor (3IG)
	2g1s	Ketopiperazine-Based Inhibitor (4IG)
	2g1y	Ketopiperazine-Based Inhibitor (5IG)
	2g20	Ketopiperazine-Based Inhibitor (L1A)
	2g21	Ketopiperazine-Based Inhibitor (L1B)
	2g22	Ketopiperazine-Based Inhibitor (6IG)
	2g24	Ketopiperazine-Based Inhibitor (7IG)
	2g26	Ketopiperazine-Based Inhibitor (3LG)
	2g27	Ketopiperazine-Based Inhibitor (4LG)
	2i4q	PF02342674
	2iko	Ketopiperazine-Based Inhibitor (7IG)
	2iku	LIY
	2il2	LIX
	2v0z	ALISKIREN
	2v10	Inhibitor 9
	2v11	Inhibitor 6
	2v12	Inhibitor 8
	2v13	Inhibitor 7
	2v16	Inhibitor 3
	3d91	Remikiren
	3gw5	Alkylamine inhibitor
	3g6z	Bioavailable Inhibitor
	3g70	Bioavailable Inhibitor
	3g72	Bioavailable Inhibitor
	3km4	Bioavailable Alkyl Amine Inhibitor
	3k1w	Bioavailable Inhibitor
	3oqf	indole-piperazine inhibitor
	3oot	indole-piperazine inhibitor
	3oqk	indole-piperazine inhibitor
	3sfc	Azaindole-3-Carboxamide
	3oad	Piperidine inhibitors
	3oag	Piperidine inhibitors
	3o9l	Piperidine inhibitors
	3own	Macrocyclic inhibitor
	3q3t	Alkyl Amine Inhibitor
	3q4b	Alkyl Amine Inhibitor
	3q5h	Alkyl Amine Inhibitor
Renin-Agt	2x0b	Complexed together
Ang I	1n9u	Solution structure
ACE N-term	2c6f	Native
	2c6n	Lisinopril
	2xyd	Phosphinic Tripeptide
	3nxq	RXP407 / Glycsoylation mutant (Ndom389 / minimal for expression)
ACE C-term	1o8a	Native
	1o86	Lisinopril
	2ydm	Selenium analogue of Captopril
	1uzf	Captopril
	iuze	Enalaprilat
	2oc2	RXPA380
	2iux	G1234 mutant
	2iul	G13 mutant
	2xy9	Phosphinic Tripeptide
	3bkk	Ketone ACE inhibitor kAF
	3bkl	Ketone ACE inhibitor kAW
	3l3n	lisW
	4aph	Ang II
	4apj	BPPb
Ang II	1n9v	Solution structure
ACE2	1r42	Native
	1r4l	MLN-4760
	3sci	spike protein from SARS coronavirus (human) complexed
	3scj	spike protein from SARS coronavirus (civet) complexed
	2ajf	spike protein from SARS coronavirus complexed
	3d0g	2002-2003 spike protein from SARS coronavirus (human) complexed
	3d0h	2002-2003 spike protein from SARS coronavirus (civet) complexed
	3d0i	2005-2006 spike protein from SARS coronavirus (civet) complexed
	3sck	spike protein from SARS coronavirus (civet) complexed
	3scl	spike protein from SARS coronavirus (epidemic strain) complexed
	3kbh	NL63 respiratory coronavirus
Ang-(1-7)	2jp8	Solution structure
Neprilysin	1r1h	Crystal structure of Nep (1.95 Å resolution)
PRCP	3n2z	Crystal structure of Prolylcarboxypeptidase (2.8 Å Resolution)

Table S1 Known PDB protein structures of the renin angiotensin system

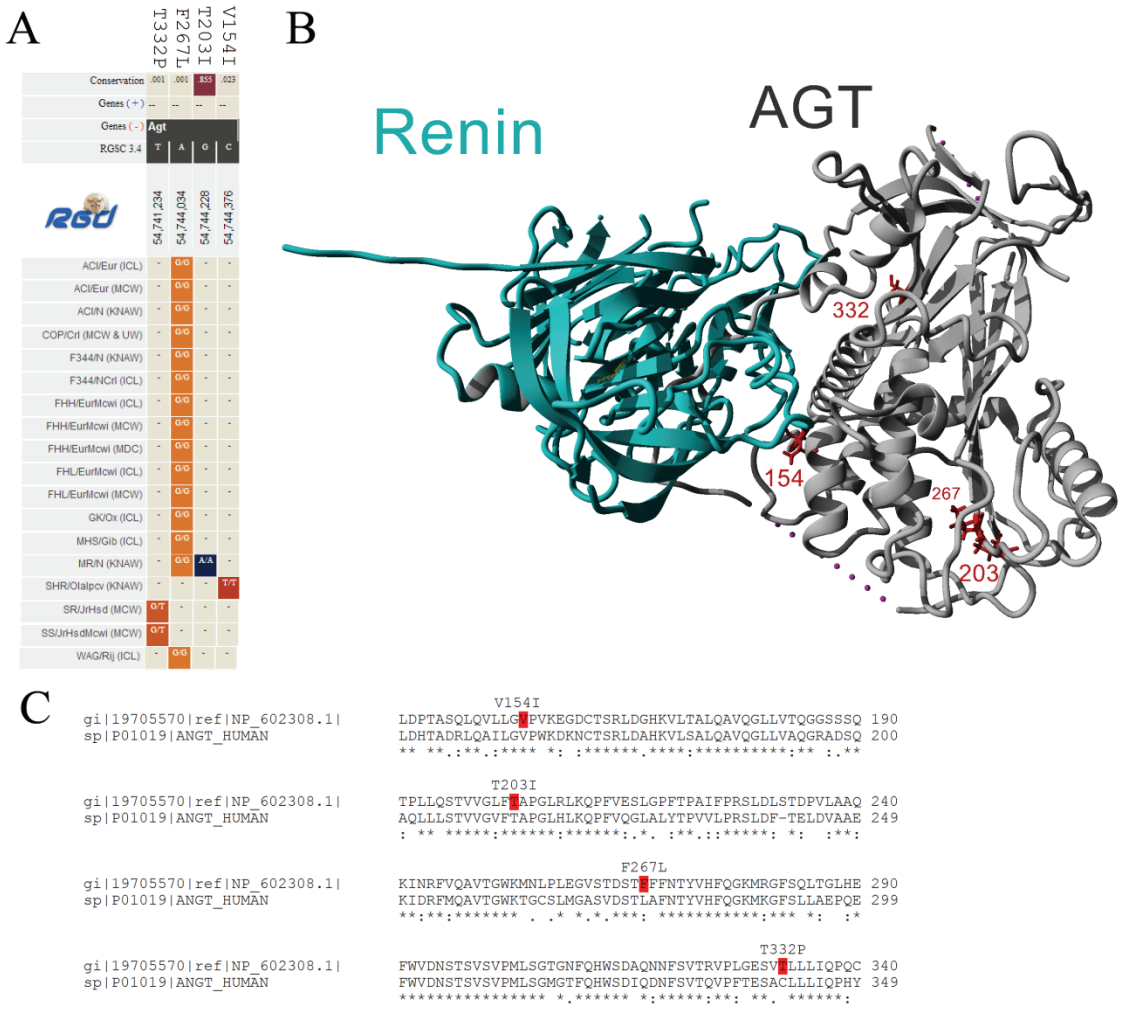

Figure S1 Variations in rat Angiotensinogen (AGT). Nonsynonymous variations found in Angiotensinogen in the 51 curated rat genomes of the MCW RGD database. **A**) Four amino acids were identified to have variations (mostly homozygous changes, G/G, as opposed to heterozygous, G/T) from the reference rat genome alleles (gray box) leading to amino acid changes identified on the top. **B**) Each amino acid was mapped onto the structure of Renin-AGT interaction. Amino acid 154 is found on the binding interface of the two proteins, while 203 and 267 were clustered in internal packing. **C**) Sequence alignment of the reference rat sequence with human, showing conservation of 154 and 203. This suggests that the change to amino acid 154 from a valine to an isoleucine may have functional alterations in the interaction between AGT and Renin.

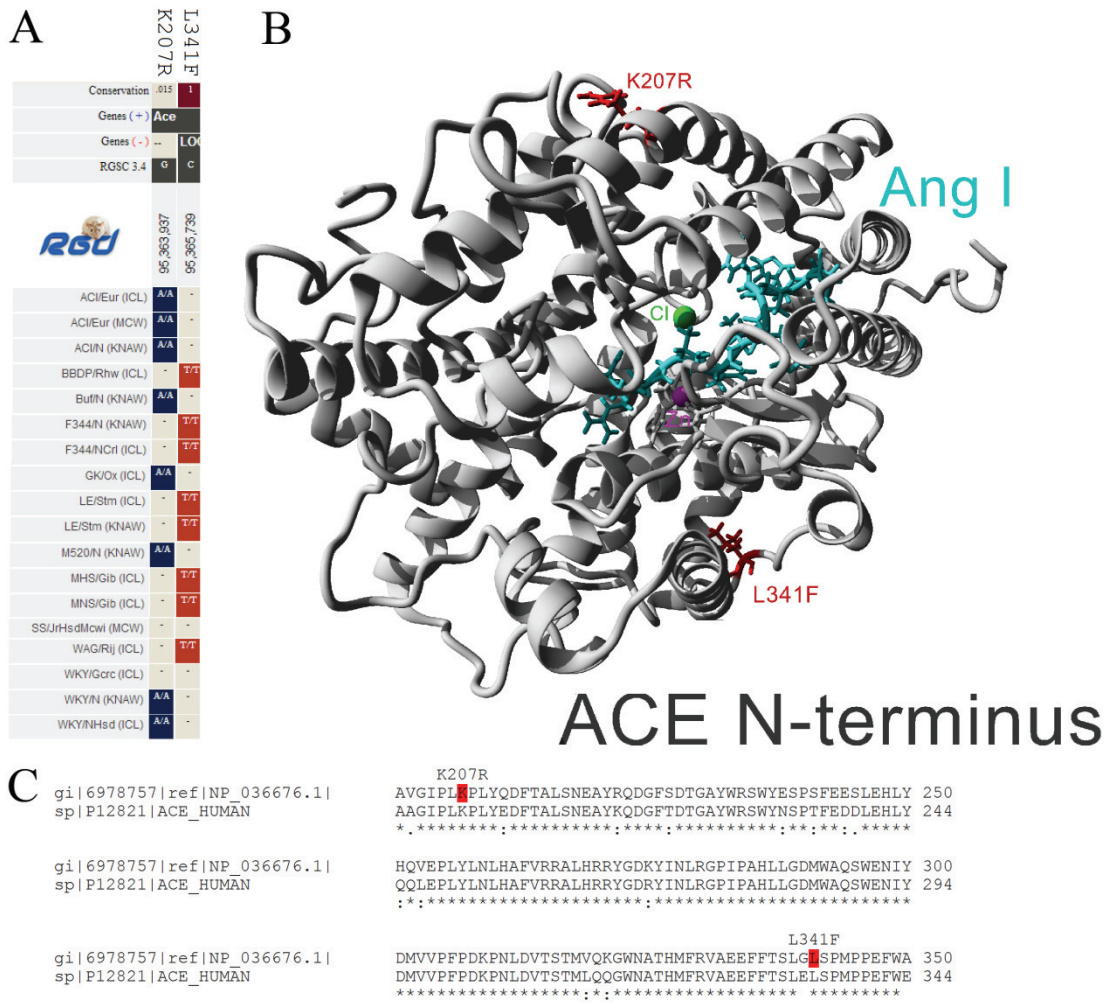

Figure S2 Variations in rat ACE. Nonsynonymous variations found in ACE in the 51 curated rat genomes in the MCW RGD database. **A**) Two amino acids were identified to have variations from the reference rat genome alleles (gray box) leading to amino acid changes identified on the top. **B**) Each amino acid was mapped onto the structure of the native ACE N-terminus (gray). Both amino acid changes are outside of the Zn active site (magenta) and Ang I (cyan) binding. **C**) Sequence alignment of the reference rat sequence with human, showing conservation of 207 and 341. These amino acids may alter the interaction of the N-terminus with the C-terminus or other yet to be identified proteins, but these contacts are beyond the assessment of this study.

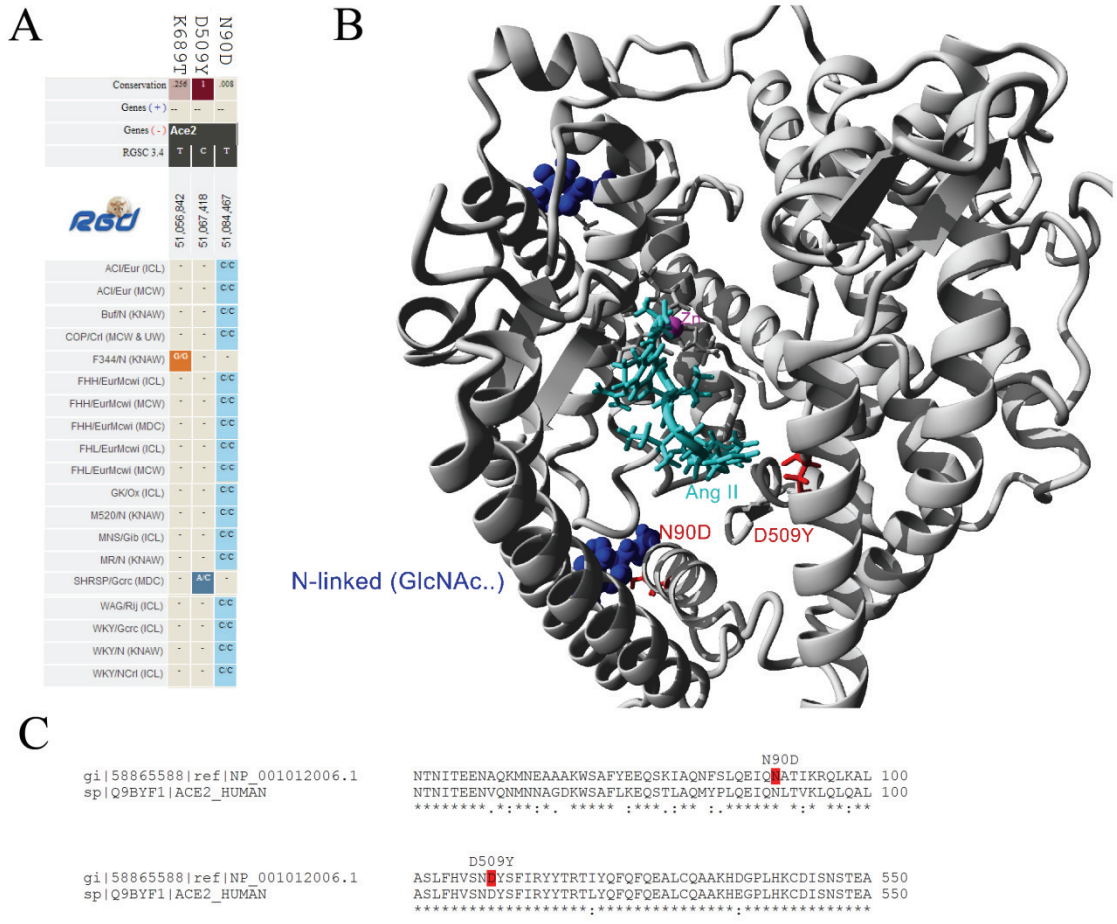

Figure S3 Variations in rat ACE2. Nonsynonymous variations found in ACE2 in the 51 curated rat genomes in the MCW RGD database. **A**) Three amino acids were identified to have variations from the reference rat genome alleles (gray box) leading to amino acid changes identified on the top. Two of these variations mapped to the main enzyme domain. **B**) Each amino acid was mapped onto the structure of the native ACE2 (gray). Amino acid 90 is known to contain an N-linked glycosylation important for cell secretion. The second amino acid change (509) occurs close to the Zn active site (magenta) and Ang II binding (cyan) located on the second arm of ACE2. These both have a high probability of altering enzyme function. **C**) Sequence alignment of the reference rat sequence with human, showing conservation of 90 and 509. All of this data suggest a high probability for alterations in function due to these variations.

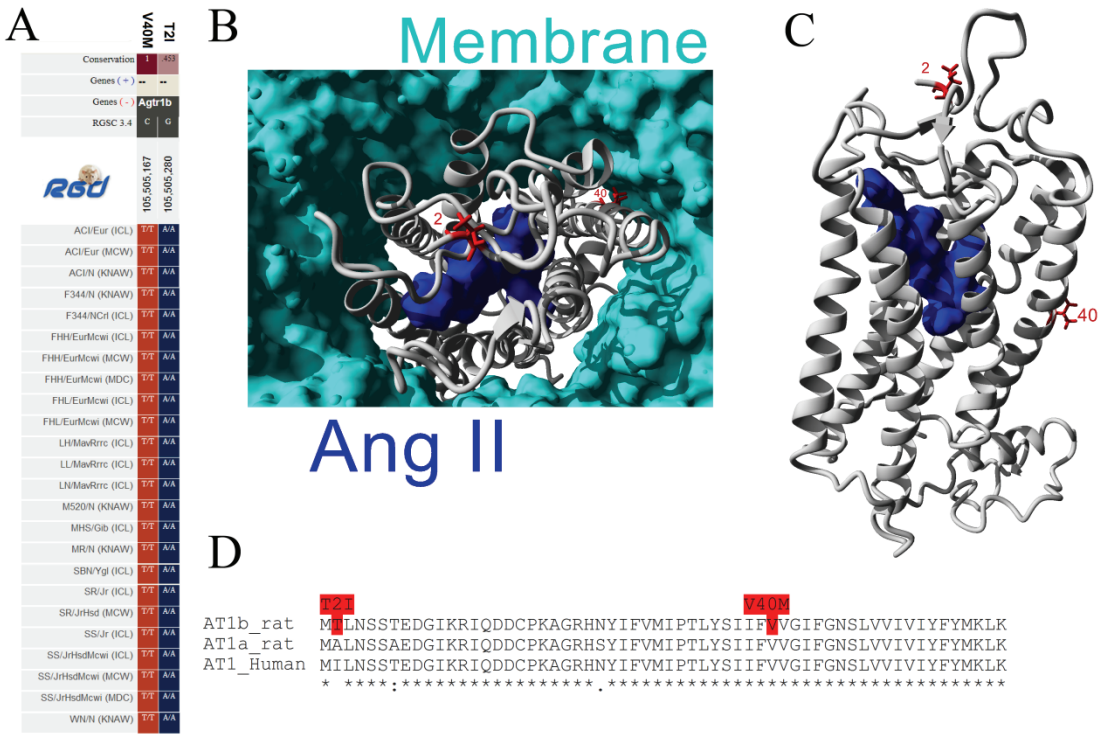

Figure S4 Variations in rat AT1b. Nonsynonymous variations found in AT1b in the 51 curated rat genomes in the MCW RGD database. **A**) Two amino acids were identified to have variations from the reference rat genome alleles (gray box) leading to amino acid changes identified on the top. **B-C**) Each amino acid was mapped onto the modeled structure of AT1 with (**B**) or without (**C**) a lipid membrane. Amino acid 2 is found in the N-terminal segment while 40 is located in the middle of helix 1 at a site of membrane (cyan) contact. Changes to amino acid 40 have the potential to result in restructuring of the helix and alteration of contact with the Ang II peptide (blue). **D**) Sequence alignment of the rat AT1a and AT1b of rat to AT1 of human, showing conservation of amino acid 40 and not 2. This suggests that amino acid 40 variations may alter the function of AT1b.

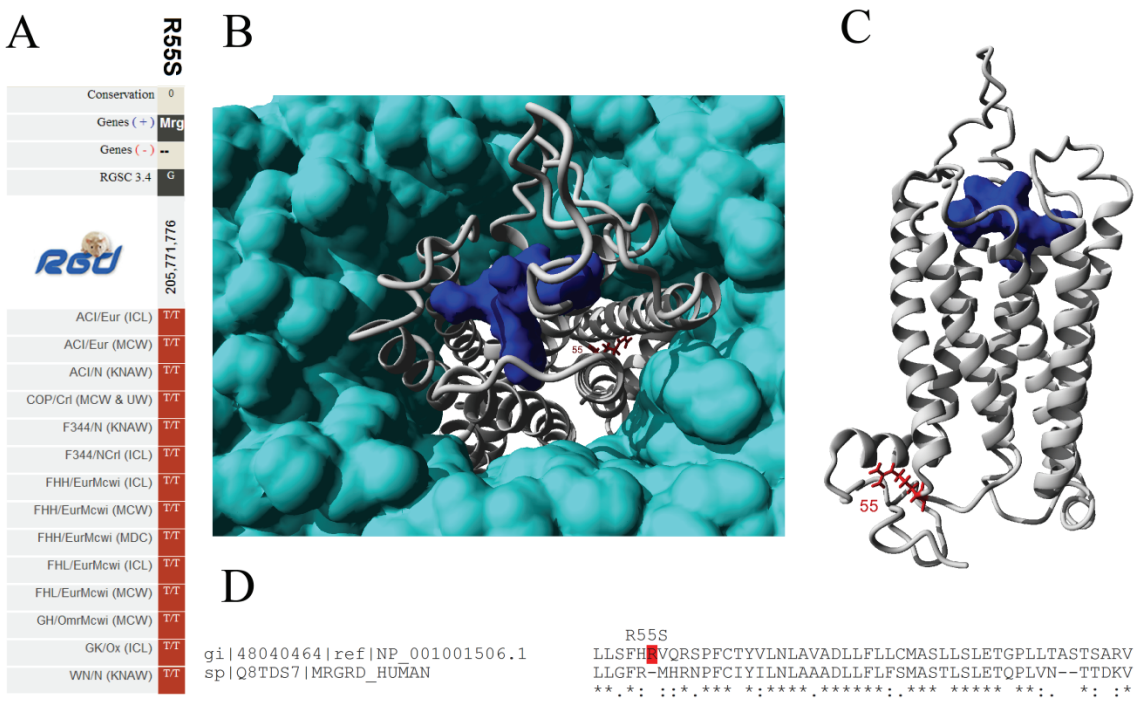

Figure S5 Variations in rat MRGD. Nonsynonymous variations found in MRGD in the 51 curated rat genomes in the MCW RGD database. **A**) One amino acid was identified to have variation from the reference rat genome allele (gray box) leading to amino acid change identified on the top. **B-C**) This amino acid was mapped onto the modeled structure of MRGD with (**B**) or without (**C**) a lipid membrane. Amino acid 55 is found on the intracellular end of the first helix. **D**) Sequence alignment of the reference rat with human, showing variation at amino acid 55. This suggests minimal role of variation at this site.

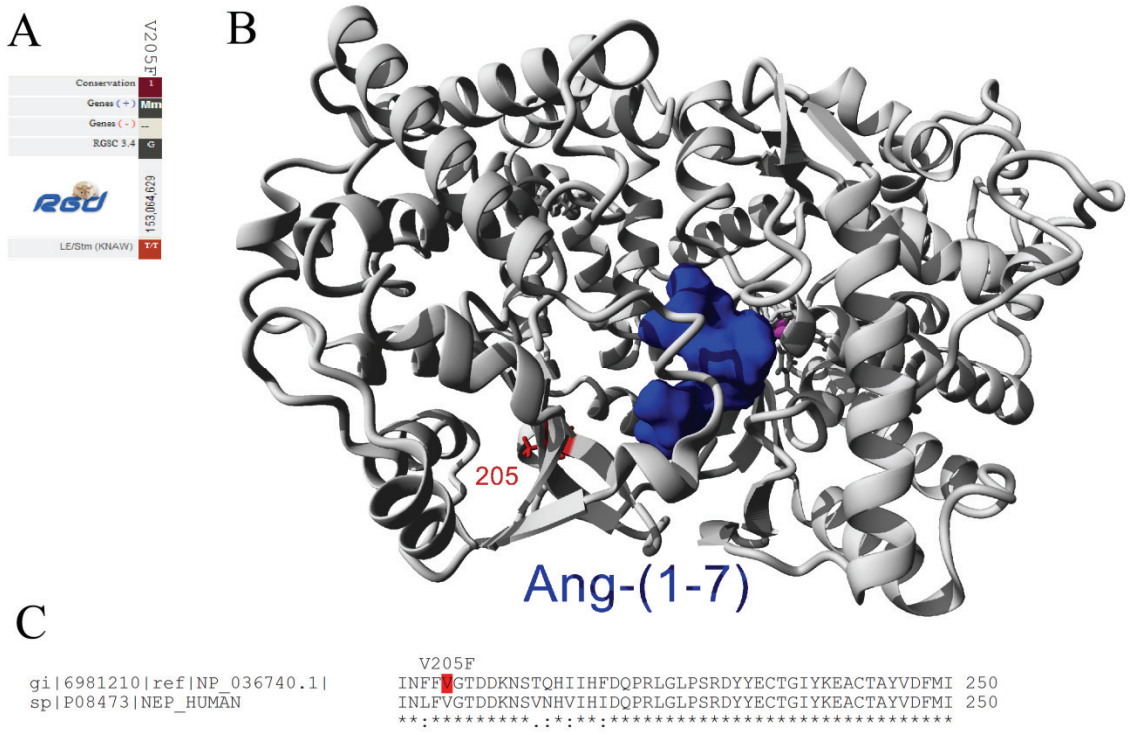

Figure S6 Variations in rat Neprilysin. Nonsynonymous variations found in Neprilysin (from the *MME* gene) in the 51 curated rat genomes in the MCW RGD database. **A**) One amino acids was identified to have variation from the reference rat genome allele (gray box) leading to amino acid change identified on the top. **B**) Amino acid 205 is located away from the Zn active site (magenta) and Ang-(1-7) binding based on the structures for Neprilysin. **C**) Sequence alignment of the reference rat sequence with human, showing conservation of amino acid 205. This data suggests a high probability for slight alterations in domain packing due to the increase bulk of the phenylalanine side chain as opposed to the valine, but minimal contributions of altering the Zn binding region and function of the protein.

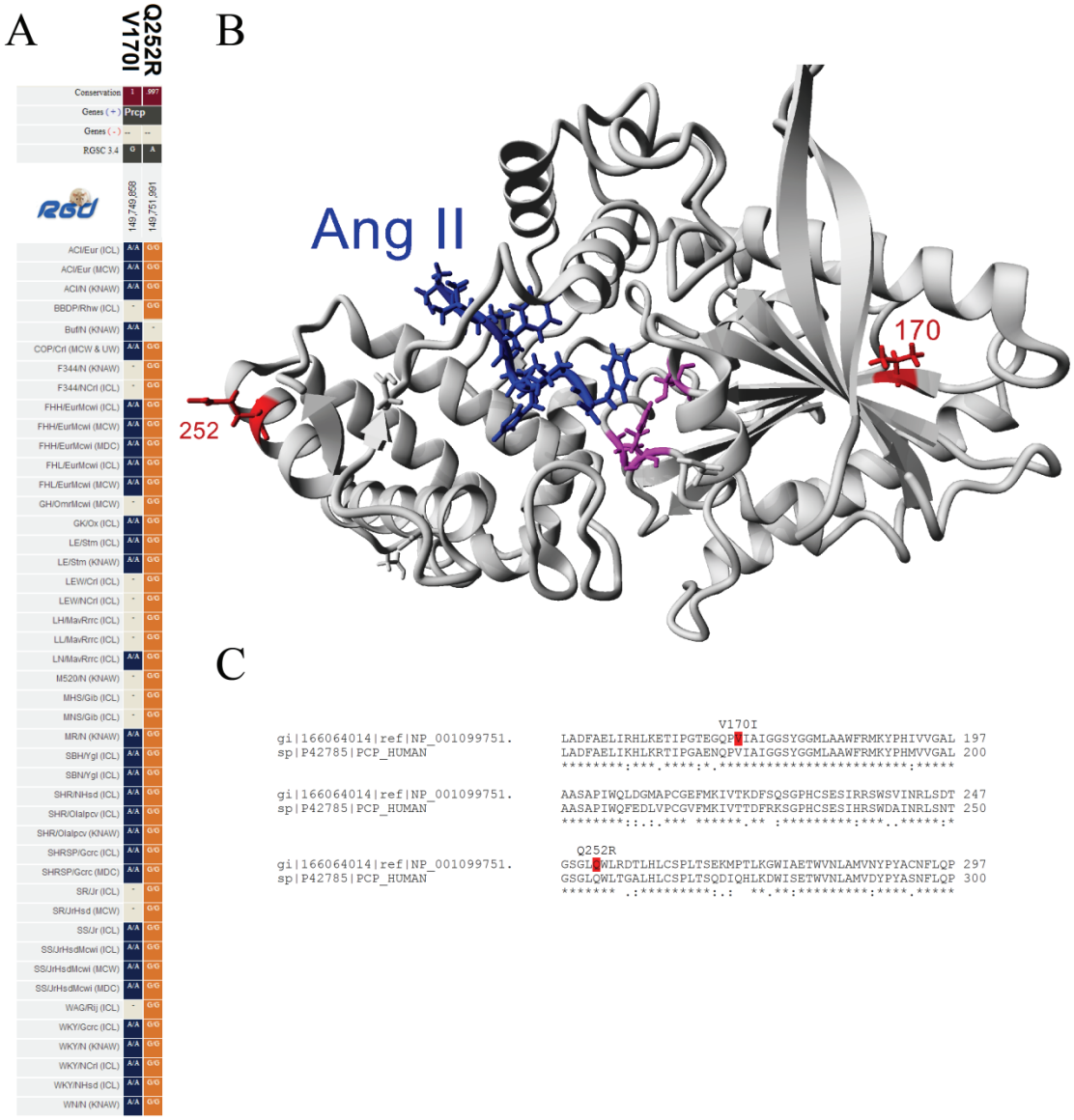

Figure S7 Variations in rat PRCP. Nonsynonymous variations found in PRCP in the 51 curated rat genomes in the MCW RGD database. **A**) Two amino acids were identified to have variations from the reference rat genome allele (gray box) leading to amino acid changes identified on the top. **B**) Each amino acid was mapped onto the structure of the PRCP, both away from the active site residues (magenta) and Ang II (blue) binding. **C**) Sequence alignment of the reference rat sequence with human, showing conservation of 170 and 252. Amino acid 170 would likely maintain proper hydrophobic packing with the V170I change. The Q252R has the potential to alter the surface environment for altered interactions with proteins outside the scope of this study.