

Shifting paradigm from gene expressions to pathway reveals causes of physiological mechanisms in blood pressure control by quantitative trait loci

Alan Y. Deng, Annie Menard and David W. Deng

Research Centre, CRCHUM (Centre hospitalier de l'Université de Montréal), Department of Medicine,
Université de Montréal, Montréal, Québec, Canada

Table Supplementary S1 (Table S1): Rat QTLs and genes residing in the chromosome intervals harboring them that correspond to human GWAS genes functionally captured by congenic knock in genetics.

<u>Rat QTL</u>	<u>Rat Gene</u>	<u>Rat Chr spans</u>	<u>Human GWAS gene</u>	<u>Human CHR</u>
<u><i>C1QTL1</i></u>	<u><i>Fndc1</i></u>	48905631..48987877	<u><i>FNDC1</i></u>	6
<i>C1QTL2</i>	<i>Pepd</i>	91925878..92416063	<i>PEPD</i>	19
	<i>Mybpc2</i>	101572091..101595585	<i>MYBPC2</i>	19
	<i>Rras</i>	102077775..102081673	<i>RRAS</i>	19
	<i>Snrnp70</i>	102431122..102468602	<i>SNRNP70</i>	19
	<i>Kcnj11</i>	103186859..103190535	<i>KCNJ11</i>	11
	<i>Atp10a</i>	117144423..117311749	<i>ATP10A</i>	15
	<i>Qpctl</i>	81314398..81323907	<i>QPCTL</i>	19
	<i>Gipr</i>	81329939..81340229	<i>GIPR</i>	19
	<i>Apoe</i>	81878372..81882298	<i>APOE</i>	19
	<i>B9d2</i>	83735237..83741209	<i>B9D2</i>	19
	<i>Akt2</i>	85617612..85667423	<i>AKT2</i>	19
	<i>Fbxo17</i>	88084918..88100373	<i>FBXO17</i>	19
	<i>Sars2</i>	88104901..88116638	<i>SARS2</i>	19
	<i>Tshz3</i>	93825005..93896330	<i>TSHZ3</i>	19
	<i>Ccne1</i>	95575136..95584387	<i>CCNE1</i>	19
<i>C1QTL3</i>	<i>Mef2a</i>	129273893..129407071	<i>MEF2A</i>	15
	<i>Mctp2</i>	134362777..134596330	<i>LOC400456</i>	15
	<i>Chd2</i>	135782462..135897354	<i>CHD2</i>	15
	<i>Akap13</i>	138007112..138312524	<i>AKAP13</i>	15
	<i>Klhl25</i>	138322710..138355032	<i>KLHL25</i>	15
	<i>Idh2-Sema4b</i>	142830040..143153628	<i>IDH2[21861]-SEMA4B</i>	15
	<i>Furin-Fes</i>	14312727..143136513	<i>FURIN-FES</i>	15
	<i>Zscan2</i>	143630849..143646301	<i>ZSCAN2</i>	15
	<i>Wdr73</i>	143663956..143672463	<i>WDR73</i>	15
	<i>Nmb</i>	143673434..143676833	<i>NMB</i>	15
	<i>Pde8a</i>	143980312..144102752	<i>PDE8A</i>	15
	<i>Tm6sf1</i>	144601683..144647599	<i>TM6SF1</i>	15
	<i>Adamtsl3</i>	145170122..145490045	<i>ADAMTSL3</i>	15
	<i>Abhd17c</i>	147177240..147218200	<i>ABHD17C</i>	15
	<i>Nox4</i>	157246099..157285107	<i>NOX4</i>	15
	<i>Gab2</i>	168423264..168486051	<i>GAB2</i>	11
	<i>Usp35</i>	168490390..168514120	<i>USP35</i>	11
	<i>Clns1a</i>	168883031..168903326	<i>CLNS1A</i>	11
	<i>Thap12</i>	169866610..169882330	<i>C11orf30</i>	11
	<i>Pold3</i>	171284462..171323431	<i>POLD3</i>	11
	<i>Fam168a</i>	171925433..172078008	<i>FAM168A</i>	11
	<u><i>Relt</i></u>	172081904..172099491	<u><i>RELT (C1QTL5RELT)</i></u>	11
	<i>Arhgef17</i>	172105535..172164079	<i>ARHGEF17</i>	11
	<i>P2ry6</i>	172169438..172204831	<i>P2RY6</i>	11
	<i>Clpb</i>	172929476..173055807	<i>CLPB</i>	11

	<i>Phox2a</i>	173083448..173087966	<i>PHOX2A</i>	11
	<i>Cckbr</i>	177269044..177279480	<i>CCKBR</i>	11
	<i>Lmo1</i>	180718642..180753931	<i>LMO1</i>	11
	<i>St5</i>	181125790..181275226	<i>ST5</i>	11
	<i>Arntl</i>	185007527..185105413	<i>ARNTL</i>	11
	<i>Adm</i>	182433109..182435280	<i>ADM</i>	11
	<i>Nucb2</i>	192078545..192115045	<i>NUCB2</i>	11
	<i>Plekha7</i>	192397589..192463974	<i>PLEKHA7</i>	11
	<i>Sox6</i>	192644288..193155831	<i>SOX6</i>	11
	<u>Umod</u>	196127939..196141822	<u>UMOD</u> (C1QTL6UMOD)	16
	<i>Tnrc6a</i>	200079394..200206235	<i>TNRC6A</i>	16
	<i>Fbxl19</i>	206218078..206238886	<i>FBXL19</i>	16
	<u>Bag3</u>	206989244..207013177	<u>BAG3</u> (C1QTL7BAG3)	10
	<i>Fgfr2</i>	207626732..207731841	<i>FGFR2</i>	10
	<i>Htra1</i>	208532013..208581538	<i>HTRA1</i>	10
	<i>Ctbp2</i>	211993864..212023075	<i>CTBP2</i>	10
	<i>Ppp2r2d</i>	218132463..218166450	<i>PPP2R2D</i>	10
	<i>Bnip3</i>	218174697..218191883	<i>BNIP3</i>	10
	<i>Inpp5a</i>	218656022..218844837	<i>INPP5A</i>	10
	<i>Cracr2b</i>	220920617..220926199	<i>CRACR2B</i>	11
	<i>H19</i>	222639223..222641899	<i>H19</i>	11
	<i>Ano1</i>	224612597..224760421	<i>ANO1</i>	11
	<i>Sipa1</i>	227941623..227953709	<i>SIPA1</i>	11
	<i>Ehbp1l1</i>	227997200..228017390	<i>EHBP1L1</i>	11
	<i>Cox8a</i>	229457144..229459465	<i>COX8A</i>	11
	<i>Lrrc10b</i>	233448290..233449518	<i>LRRC10B</i>	11
	<u>Cbwd1</u>	250092601..250135008	<u>CBWD1</u> (C1QTL8CDK)	9
	<u>Dock8</u>	250200507..250417771	<u>DOCK8</u>	9
	<u>Kank1</u>	250464788..250659569	<u>KANK1</u>	9
	<i>Glis3</i>	253622178..254039761	<i>GLIS3</i>	9
	<i>Pten-Rnls</i>	258651829..258717009- 259052388..259324901	<i>PTEN-RNLS</i>	10
	<i>Hhex</i>	263583988..263589575	<i>HHEX</i>	10
	<i>Plcel</i>	264652842..264956664	<i>PLCE1</i>	10
C18QTL2	<i>Tmco6</i>	29282952..29289547	<i>TMCO6</i>	5
	<i>Ndufa2</i>	29289478..29291567	<i>NDUFA2</i>	5
	<i>Ik</i>	29291708..29306512	<i>IK</i>	5
	<i>Wdr55</i>	29309024..29312537	<i>WDR55</i>	5
	<i>Dnd1</i>	29312395..29315019	<i>DND1</i>	5
	<i>Hars</i>	29315352..29332458	<i>HARS</i>	5
	<i>Hars2</i>	29332574..29341926	<i>HARS2</i>	5
	<i>Zmat2</i>	29343457..29348092	<i>ZMAT2</i>	5
	<i>Pcdha1</i>	29648344..29924443	<i>PCDHA1</i>	5
	<i>Pcdha2</i>	29657322..29924443	<i>PCDHA2</i>	5
	<i>Pcdha3</i>	29663495..29924443	<i>PCDHA3</i>	5
	<i>Pcdha4</i>	29670058..29924443	<i>PCDHA4</i>	5
	<i>Pcdha5</i>	29677518..29924444	<i>PCDHA5</i>	5
	<i>Pcdha6</i>	29684456..29924443	<i>PCDHA6</i>	5

	<i>Pcdha7</i>	29690611..29924443	<i>PCDHA7</i>	5
	<i>Prr16</i>	45166501..45372242	<i>PRR16</i>	5
	<i>Ftmt-Srfbp1</i>	46510407..46690474	<i>FTMT-SRFBP1</i>	5
	<i>Prdm6</i>	47648048..47750565	<i>PRDM6</i>	5
	<i>Csnk1g3</i>	48043786..48126393	<i>CSNK1G3</i>	5
	<i>Slc12a2</i>	52104434..52172638	<i>SLC12A2</i>	5
	<i>Fbn2</i>	52284482..52487739	<i>FBN2</i>	5
<i>C18QTL3</i>	<i>Fbxo38</i>	57053464..57100790	<i>FBXO38</i>	5
	<i>Spink7</i>	57142773..57146245	<i>SPINK7</i>	5
	<i>Piezo2</i>	57576278..57949635	<i>PIEZO2</i>	18
	<i>Wdr7</i>	58326473..58612197	<i>WDR7</i>	18
	<i>Neddd4l</i>	59595643..59921504	<i>NEDD4L</i>	18
<i>C18QTL4</i>	<i>Slc14a2</i>	74185426..74617691	<i>SLC14A2</i>	18
	<i>Setbp1</i>	74772163..74960529	<i>SETBP1</i>	18
	<i>Tshz1</i>	79910848..79956064	<i>TSHZ1</i>	18

Fig. 1 of the text defines the chromosome regions containing QTLs and the gene residing in the intervals containing these QTLs. Human GWAS genes are from (Evangelou et al., 2018). Only the genes underlined were analyzed further in the current work, because they are functional candidate genes for the human QTLs. ***Arhgap12***, Rho GTPase activating protein 12; ***Arhgef17***, Rho guanine nucleotide exchange factor 17; ***Bag3***, BAG cochaperone 3; ***Cbwd1***, COBW domain containing 1; ***Dnd1***, DND microRNA-mediated repression inhibitor 1; ***Dnmt3b***, DNA methyltransferase 3 beta; ***Fndc1***, fibronectin type III domain containing 1; ***Kank1***, KN motif and ankyrin repeat domains 1; ***Dock8***, dedicator of cytokinesis 8; ***Plce1***, phospholipase C, epsilon 1; ***Procr***, protein C receptor; ***Relt***, RELT, TNF receptor; ***Rreb1***, ras responsive element binding protein 1; ***Umod***, uromodulin; ***Zscan2***, zinc finger and SCAN domain containing 2. CHR, Chromosome.

Table Supplementary S2 (Table S2): Mutation survey of genes in rat QTL-residing intervals that capture human GWAS genes by congenic knock in genetics

Rat QTL name	Rat/human GWAS Gene	Mutation detected Lew/ DSS	Change in amino acid (AA) Lew/DSS	RGD (AA) Lew/DSS	Human GWAS SNP
<u>C1QTL1</u>	<i>FNDC1</i>	C282T C1155T T1169C C1174T A1330G G2526T C2900G C3198G G3447A C4121T C4140G A4158G C4197T T4437C T4450C	No No M390T P392S N444D No P967R No No P1374L No No No No No	M390T P392S N444D No P1475L	Intergenic rs449789
<u>C1QTL2</u>	<i>Thz3</i>	C2784T	No	No	
<u>C1QTL3</u>	<i>Mctp2</i>	C474T T558C G1017A C2457A	No No No No	No No No No	
	<i>Akap13</i>	3'UTR	No	No	
	<i>Idh2</i>	3'UTR	No	No	
	<i>Sema4b</i>	A1203G A1419G	No No	No No	
	<i>Fes</i>	C717T	No	No	
	<i>Furin</i>	C1066T	No	No	
	<i>Zscan2</i>	No	No	E155K unconfirmed	rs3825877 intergenic
	<i>Pde8a</i>	T1410C	No	No	
	<i>Gab2</i>	T152C	No	No	
	<i>Clns1a</i>	5'UTR 3'UTR	No No	No No	
	<i>Prkrir</i>	3'UTR	No	No	
	<i>Fam168a</i>	T552C	No	No	
	<u>Relt</u>	G214A C522G	G72S No	G72S No	rs7115605 (intergenic)
	<i>Arhgef17</i>	No	No	G1016S unconfirmed	rs11827650 (intronic)
	<i>P2ry6</i>	3'UTR	No	No	
	<i>P2ry2</i>	5'UTR T999C	No No	No No	

		3'UTR	No	No	
	<i>Phox2a</i>	T360C	No	No	
	<i>Dennd2b</i> (<i>St5</i>)	C2457T	No	No	
	<i>Arntl</i>	5'UTR	No	No	
	<i>Nucb2</i>	G150A T1176C	No No	No No	
	<u>Umod</u>	C51T G253A C464T C469G C669A T994C T1422C	No V85M S155F E157Q (unconfirmed) No I326V No	No V85M S155F No No I326V No	rs13333226 (intronic)
	<i>Tnrc6a</i>	3'UTR	No	No	
	<i>Fbxl19</i>	3'UTR	No	No	
	<u>Bag3</u>	C957T C994T T1225C A1256C T1332C	No P332S S409P H419P No	No P332S S409P H419P No	rs72842207 (intronic)
	<i>Fgfr2</i>	3'UTR	No	No	
	<i>Ctbp2</i>	3'UTR	No	No	
	<i>Ppp2r2d</i>	A468G	No	No	
	<i>Bnip3</i>	3'UTR	No	No	
	<i>Inpp5a</i>	G994A	No	No	
	<i>H19</i>	No cDNA	No	No	
	<u>Cbwd1</u>	G242A	S81N	S81N	rs2992854 (intergenic)
	<u>Dock8</u>	G437A T1797G C2027T G3675A T3876C G4296A C4365T T4413C	R146K No No No No No No No	R146K No No No No No No No	rs643058 (intergenic) rs520015 (intronic) rs604470 (intronic)
	<u>Kank1</u>	C210T C567T A1463G T1616C C1701T T1983C C2465G G3126A G3902G	No No No M539T No No P822R No S1301N	No No No M539T No No P820A No S1299N	rs17369029 (3'UTR) rs16923342 (intergenic) rs60191654 (intergenic)
	<i>Plcel</i>	T2103C C3522T	No No	No No	rs932764 (intronic)

		T3597C C3675T G3697A	No No Ala1233Thr (unconfirmed)	No No No	
<u>C18QTL2</u>	<i>Tmco6</i>	5'UTR	No	No	
	<i>Ndufa2</i>	G135A	No	No	
	<i>Ik</i>	T342C	No	No	
	<i>Dnd1</i>	C864T G866A G877A	No 289Stop (unconfirmed) No	No No No	rs2530243 (intronic) rs2563333 (synonymous)
	<i>Hars2</i>	C1431T	No	No	
	<i>Pcdha1</i>	Not sure		Not sure	
	<i>Pcdha2</i>	Not sure		Not sure	
	<i>Pcdha3</i>	Not sure		Not sure	
	<i>Pcdha4</i>	Not sure		Not sure	
	<i>Pcdha5</i>	Not sure		Not sure	
	<i>Pcdha6</i>	Not sure		Not sure	
	<i>Pcdha7</i>	Not sure		Not sure	
	<i>Prr16</i>	A84G	No	Not sure	
	<i>Csnk1g3</i>	T461C C689T	No No	No No	
	<i>Slc12a2</i>	G462A G2187A	No No	No No	
	<i>Fbn2</i>	T741C A3710G C3704T C3986T C4781G C5882T A8533G T8534C	No No No No No No No No	No No No No No No No No	
<u>C18QTL4</u>	<i>Neddl4</i>	A321T T1995C A2139G	No No No	No No No	

Gene locations are indicated on the map in Fig. 1. The position of a mutation enumerates from the ATG start codon of that gene. The amino acid position begins from the first methionine. *Arhgap12*, Rho GTPase activating protein 12; *Arhgef17*, Rho guanine nucleotide exchange factor 17; *Bag3*, BAG co-chaperone 3; *Cbwd1*, COBW domain containing 1; *Dnd1*, DND microRNA-mediated repression inhibitor 1; *Dnmt3b*, DNA methyltransferase 3 beta; *Fndc1*, fibronectin type III domain containing 1; *Kank1*, KN motif and ankyrin repeat domains 1; *Dock8*, dedicator of cytokinesis 8; *Plce1*, phospholipase C, epsilon 1; *Procr*, protein C receptor; *Relt*, RELT, TNF receptor; *Rreb1*, ras responsive element binding protein 1; *Umod*, uromodulin; *Zscan2*, zinc finger and SCAN domain containing 2. No Copy Number Variation (CNV) had been found for those genes from total genome sequencing of DSS and Lewis rats based on our current work and those of the rat genome database. RGD, public rat genome base.

Table Supplementary S3 (Table S3): Survey of non-coding GWAS SNP conservations/homology during primate evolution

More recent  More ancient

Human SNP/ Marked gene	Chimpanzee (6.4 MYA)	Bonobo (6.4 MYA)	Gorilla (8.6 MYA)	Orangutan (15.2 MYA)	Gibbons (19.6 MYA)	Old World monkeys (28.9 MYA)	New World monkeys (43 MYA)
rs449789/ <i>FNDC1</i> (intergenic)	homology	homology	homology	homology	homology	homology/ rhesus; No homology/ baboon	No homology
rs7115605/ <i>RELT</i> (intergenic variant)	homology	homology	homology	homology	homology	homology	Homology/ Marmoset No homology/ Squirrel Monkey; SNP absent, and the surrounding sequence is not conserved.
rs13333226/ <i>UMOD</i> (intron variant)	homology	homology	homology	homology	homology	homology	homology
rs72842207/ <i>BAG3</i> (intron variant)	homology	homology	homology	homology	homology	homology	No homology; SNP absent, but the surrounding sequence is little conserved.
rs2992854/ <i>CBWD1</i> (intergenic variant)	No homology; SNP absent, no hit on the right chr.	homology	homology	homology	homology	homology	homology
rs643058/ <i>DOCK8</i> (intergenic variant)	No homology; SNP absent, no hit on the right chr.	No homology ;SNP absent, and sequence around is not conserved.	homology	homology	homology	homology	Homology/Ma rmoset No homology/ Squirrel Monkey; SNP absent, and the surrounding sequence is not conserved.
rs520015/ <i>DOCK8</i> (intron variant)	No homology; SNP absent, no hit on the right chr.	homology	homology	homology	homology	homology	No homology; SNP absent, but the surrounding sequence is little conserved.
rs604470/ <i>DOCK8</i> (intron variant)	homology	homology	homology	homology	homology	homology	homology
rs17369029/ <i>KANK1</i> (3'UTR variant)	homology	No homology ; SNP absent, but surroundin g sequence	homology	homology	homology	homology	homology

		is little conserved.					
rs16923342/ <i>KANK1</i> (intergenic variant)	homology	homology	homology	homology	homology	No homology; SNP absent, but the surrounding sequence is much conserved.	No homology; SNP absent, but the surrounding sequence is little conserved.
rs60191654/ <i>KANK1</i> (intergenic variant)	homology	No homology ; SNP absent, no hit on the right chr.	homology	homology	homology	homology	homology

Gene names are given in the legend for Table 1. Homology indicates that the SNP and/or surrounding sequences are conserved. Old World monkeys are represented by Rhesus macaque, baboon; New World monkeys are represented by marmoset, squirrel monkey. Searches were done at <https://genome.ucsc.edu/cgi-bin/hgGateway>. MYA, millions of years in divergence to humans (<https://timetree.org/>).

Table Supplementary S4 (Table S4): Amino acid alignment and missense mutations in codons for fibronectin type III domain containing 1 (FNDC1) in humans and rats.

Human FNDC1	MAPEAGATLRAPRRLSWAALLLLAALLPVASSAAASVDHPLKPRHVKLLSTKMGLKVTWD	60
DSS rat Fndc1	-----MGLKVTWD *****	8
Human FNDC1	PPKDATSRPVEHYNIAYGKSLKSLKYIKVNAETYSFLIEDVEPGVVVYFVLLTAENHSGVS	120
DSS rat Fndc1	PPKDATSRPVEHYNIAYGKSLKSLKSIKVNAETHSFLIKDV----- *****:****:	49
Human FNDC1	RPVYRAESPPGGEWIEIDGFPIKGPFPNETVTTEKEVPNKPLRVVRSSDDRSLVAVKAP	180
DSS rat Fndc1	-----EKEVPNKPLRMVRASDDRSLVAVKAP *****:***:*****	76
Human FNDC1	RLSGAKSPRRSRGFLLGYGESGRKMNYVPLTRDERTHEIKKLASESVYVSLQSMNSQGR	240
DSS rat Fndc1	RLSGAKSPRRSRGFLLGYGESGRKMNYVPLTRDERSHEIKKLASESVYVSLQSTNSQGG *****:*****:*****:****:	136
Human FNDC1	SQPVYRAALTKRKISEEDELDPDDISVRVMSSQSVLVSVDPLVEKQKKVVASRQYTVR	300
DSS rat Fndc1	SQPVYRAALTKRKNAEEDELDPEDISVRVMSSQSVLVAWDPLVEKQKRVASRQYTVR *****:*****:*****:*****:****:*****	196
Human FNDC1	YREKGEARLDYKQIANRRVLIENLIPDVTYEFVAVRISQGERDGKWSVVFQRTPEAPT	360
DSS rat Fndc1	YREKGESARWDYKQVSNRRALVDSLIPDVTYEFVAVRISQGERDGKWSASVFQRTPEAPT *****:*****:***:***:*****:*****:*****:*****:*****	256
Human FNDC1	TAPENLVVWPVNGKPTVVAASWDALPETEGKVKEYILSYAPALKPFGAKSLTYPGDTISA	420
DSS rat Fndc1	TAPENLRVWPVNGKPTVVTVSWDALPESEGVKEYILSYAPALKPFGAKSLTFSGHTTSA *****:*****:*****:*****:*****:*****:***:***	316
Human FNDC1	LVDGLQPGERYLFKIRATNRRGLGPHSKAFIVAMPTTSSKA--DVEQNTEDNGKPEKPEPS	478
DSS rat Fndc1	LVDGLQPGERYLFKIRATNRRGQGPFSKAFIVAIPPTSSTEASVQPNGRDNGKPEKPPQ *****:*****:*****:***:***:***:*****:	376
Human FNDC1	S-PSRAPASSQHSPVPASPOGRNAKDLLDLKNKILANGGAPRKPLRAKKAEELDLQS	537
DSS rat Fndc1	SSSAPKVAASSQ----HTPSAKNVKDALSCLKNKIQTNGVAPGRTQLHSK-VGELDPQS * :*: . *** :*: . * * * ***** :* * * : **: . * . *** *	430
Human FNDC1	TEITGEEELGSRDSPMSPSDTQDQKRTLRRPSSRHGHSVVAPGRTAVRAMPALPRRECV	597
DSS rat Fndc1	TEVTGEEELDSLSPRSSRLTLNQKPLRVPSRSGHGALAPGRTPARAGLPVLSRKEGM **:*****.* ** * :* **: * * * * * .:***** .** :*. * **:*	490
Human FNDC1	DKPGFSLATQPRPGAPPSASASPAHHASTQGTSIRPSLPASLNDNLVDSDEDERAVGSL	657
DSS rat Fndc1	DRRGPSLDPHPHRVEPSASSAYHQLSS-----TDNDSVDRKEDDQ-AGSP *: * * * :*: . *****: : : * .*** * .*: .: .**	535
Human FNDC1	HPKG-----AFAQRPALSPSRQSPSSVLRDRSSVHPGAKPASARR-TPHSGAAEE	708
DSS rat Fndc1	DPKAASSGSSPKNPGRSRPTSAPSRHAASNMLRDKSRVHPGTKAASSSTRQSHSSTSEE .**, .: **: :****: * :****:* ***** * * : **.:**	595
Human FNDC1	DSSASAPPSRLSPPHGGSSRLLPQPHLSSPLSKGGKDGEDAPATNSNAPSRSTMSSSVS	768
DSS rat Fndc1	DS--SAQPSRHFPLHRGS-----STSPLSRGWKDRQDTHASSHTTSRTASS--- ** * * * * * * :****:* * *: * :*: .: * *: *	640
Human FNDC1	SHLSSRTQVSEGAEASDGESHGDRREDGGRQAEATAQTLRARPASGHFHLLEKPFAN	828
DSS rat Fndc1	---SHPSALTEGSEEDGGADSDRAEDTIRRAEATAQIQTRPGLGHFSLIRNKPFTPH * : :*: . * * :*. * * *:***** :*: . * * *:*:***: :	697
Human FNDC1	GRSPSRFISIGRPRLQSSSPQSTVPSRAHPRVPSHSDSHPKLSSGIHGDEEDEKPLPAT	888
DSS rat Fndc1	SRNPNRFPRLRGPRQLQSPVSPQSTASKVLTRPSLPASHTRPGSDVYGDGEDEEPLPAT .**,** ***** ***** *: . * * * * : .*: .: * * *:*****	757
Human FNDC1	VVNDHVPSSSRQPIISRGWEDLRRSPQRGASLHRKEPIPENPKSTGADTHPQGYSSLASK	948
DSS rat Fndc1	VINDRTPSYPRHPISGSSDTLRRGPQRGASLYRKEPIPENSKAAGADVPPGGR-SPLSSK *:***:* * :*** . : * * .*****:***** *:***. * *: * * :*	816
Human FNDC1	AQDVQQTADTEGHSPKAQPGSTDRHASPARPPAARSQQHP--SVPRRMTPRAPQQP	1006
DSS rat Fndc1	AQGFFQQT---DEGAPQTSAPSTRQPSPARPPASRSQSPGSTVPRRMTPRDSSELS- **..**** : :*: . * . * .: *****:*** * :*****.*: . :	872
Human FNDC1	PPPVATSQHHPGPQSRDAGRSPSQPRLSLTQAGRPRPTSQGRSHSSSDPYTASSRGMLT	1066
DSS rat Fndc1	-----SSQSKDRSLSQPKLSVAHAGH-----DHPHTANSRGVLPS *:. . * * * * *:***:***: .*:***:***:***:	907

[illegible]

Table Supplementary S5 (Table S5): Amino acid alignment and missense mutations in codons for RELT TNF receptor (RELT) in humans and rats

Human_RELT	MKPSLLCRPLSCFLMLLPWPLATLTSTTLWQCPPGEEPDLDPGQGTLCRCPPGTFSAAW	60
DSS_Rat_RelT	MKRTLLCWPLSCLFVLLPWPLATPTPITPWLCPPGTEPDPDGQGTLCRTCPPGTFSASL ** :*** ***:;.:***** * * * ** * ** * ** * ** * ** * ** * ** * ** * ** * ** *	60
Human_RELT	GSSPCQPHARCSLWRRLEAQVGMATRDITLCGDCWPGWFGPWGVPVRVPCQPCSWAPLGTHG	120
DSS_Rat_RelT	DSYPCQPHYRC LQKRLEAQGATATHTVCGDCQRGWFGPQGVPHVPCQPCSKATPSTSD . * ** * ** * ** * :***** * ** **:;***** ** * ** * ** * ** * ** * ** * . * .	120
Human_RELT	CDEWGRRRARGVEVAAGASSGGETRQPGNGTRAGGPEETAAQYAVIAIIVPVFCLMGLLGI	180
DSS_Rat_RelT	CD--GRRARRGVEVAAGANSNGELRQPGNGTRAGGPEETAAQYAVIAIIVPVFCLMGLLGI ** ***** ** * . * ** ***** ** * ** * ** * ** * ** * ** * ** * ** * ** * ** *	178
Human_RELT	LVCNLLKRKGYHCTAHKEVGPFGGGGSGINPAYRTEDANEDT GVLVRLITEKKENAAA	240
DSS_Rat_RelT	LVCNLLKRKGYHCTAQKEVGPSPGGGSGINPAYRTEDANEDTIGVLVRLITEKKENAAA ***** ** * :***** . ***** ** * ** * ** * ** * ** * ** * ** * ** * ** *	238
Human_RELT	LEELLKEYHSKQLVQ TSHRPVSKLPAPPNPVPHICPHRHHLHTVQGLASLSGPCCSRCSQ	300
DSS_Rat_RelT	LEELLKEYHSKQLVQ TSHRPVPRLLPASPTPHVCPHHHLLHTVQGLASLSGPCCSRCSQ ***** ** * : * * * . ** :*** :***** ** * ** * ** * ** * ** * ** *	298
Human_RELT	KKWPEVLLSPEAVA TTPVPVSLLPNPTRVPK GAKAGRQGEITILSVGRFRVARIPEQRT	360
DSS_Rat_RelT	-KWPEVLLSPEAAAATTPAPTLLPSTSRAPKASAKPGRQGEITILSVGRFRVARIPEQRT ***** . ***** . * :*** . : * . ** * ** * ** * ** * ** * ** * ** * ** *	357
Human_RELT	SS VSE VKTITEAGPSWGDLPDSPQGPLPPEQQALLGSGGSRTKWLKPPAENKAENRYV	420
DSS_Rat_RelT	SSLLSEVKTITEAGPSEDLPESPQGPLPPEQRALLGSSGSHAKWLKPPAENKAENRYV ** :;***** . ** * :***** :***** . ** :;***** ** * ** * ** * ** *	417
Human_RELT	VRLSESNLVI 430	
DSS_Rat_RelT	VRLSESNLVI 427 *****	

* indicates amino acid identity (88%) between human and the rat. Probable human missense mutations (The Genomes Project et al., 2015) are shaded, which were curated from <https://www.ncbi.nlm.nih.gov/snp/> and as of April 23, 2020. Only those missense mutations with minor alleles that were observed at least 2 times (marked in red) in the tested populations are included with the validation status by 1000Genomes. Amino acids in blue indicate that the minor allele has been observed more than 10 times. The rat missense mutation has been experimentally confirmed and shaded in green. DSS, Dahl salt-sensitive rats.

Table Supplementary S6 (Table S6): Amino acid alignment and missense mutations in codons for uromodulin (UMOD) in humans and rats

Human_UMOD	MG-QPSLTWMLMV-VVASWFITTAATDTSEARWCSECHSNATCTEDEAVTTCQEGFTG	58
DSS_Rat_UMOD	MGQLLSLTWLLLVMMVTPWFVTAGANDSPEARRCSECHDNATCVLDGVTTCSCQAGFTG ** *****: * * * : * * . : * . * : ** * ** * . ** * . * . ** * : * * ** *	60
Human_UMOD	DGLTCVDLDECAIPGAHNCSANSSCVNTPGSFSCVCEGFRLLSPGLGCTDVDECAEPGLS	118
DSS_Rat_UMOD	DGLVCEDIDECAIPWTHNCS-NSIC NTLGSYECSCQDGFRLTPGLGCIDVNECTEQGLS ** * . * :*** * * :*** ** * * : * * * :***:*** ** * : * : * ** *	119
Human_UMOD	HCHALATCVNVVGSYLCVCPAGY RGDGWHCECSPGSCGPLDCVPEGD--ALVCADPCQA	176
DSS_Rat_UMOD	NCHSLATCVNTEGSYSVCVCPKGYRGDGYCECSPG C PGLDCLPQGPSGKLVCQDPCNV : * :***** . ** * ** * *****:***** * *****: * : * ** * ** * : .	179
Human_UMOD	HRT LDEYWRSTYEGEGYACDITDLRGWYRFVQGGMARMAETCVPLRLCNTAAPMWLNGTHP	236
DSS_Rat_UMOD	YETLTEYWRSTDYAGYSCSDMHGWYRFTGQGVMAETCVPLRLCNTAAPMWLNGSHP : . * *****: * * * : * : * :***** ***** *****:***** ** *	239
Human_UMOD	SSDEGIVSRKACAHWSGHCCCLWDASVQVKACAGGYVYNLTAPPECHLAYCTDPSSVEGT	296
DSS_Rat_UMOD	SSREGIVSRKACAHWSGHCCCLWSTEIQVKACPGGFVYNLTPEPECNLAYCTDPSSVEGT ** ***** . ***** . ***** . : :***** ** * :***** ** * :***** *****	299
Human_UMOD	CEECSIDEDCKSNNGRWHCQCKQDFNITDISLLEHRLECGANDMKVSLGKQKSLGFDK	356
DSS_Rat_UMOD	CEECGVDEDCVSDNGRWRCQCKQDFN TDVSLLEHRLECEANEIKISLSKCQLQSLGFMK ***** :***** * :*****:*****: * :***** ** * : * : * :*****:***** *	359

Human_UMOD	VFMYLSDSRCSGFNDRDN W DWVSVVT ⁴¹⁶ PARDGPCGTVLTRNETHATYSNTLYLADEIIIRD	416
DSS_Rat_UMOD	VFMYLNDRCSGFSE ⁴¹⁹ RG ⁴¹⁹ ERD ⁴¹⁹ WMSI ⁴¹⁹ VT ⁴¹⁹ PARDGPCGTVLRRNETHATYSNTLYLASEIIIRD	419
*****.* :***. :*. :***.* :***** ***** .*****		
Human_UMOD	LN ⁴⁷⁶ IKIN ⁴⁷⁶ FACSYPLDMK ⁴⁷⁶ VS ⁴⁷⁶ LKTALQPMVSALNIRVGGTGMFTV R MALFQTPSYTQPYQGSS	476
DSS_Rat_UMOD	INIRINFEC ⁴⁷⁹ SYPLDMK ⁴⁷⁹ VS ⁴⁷⁹ LKTS ⁴⁷⁹ LQPMVSALNISLGGTGKFTVQMALFQNPTYTQPYQGGS	479
:*. :*** *****.* :***** :*** **.* :***.* :***** *		
Human_UMOD	VTLSTEAFLYVGTMLDGGDL ⁵³⁶ SRFALLMTNCYATPSSNATDPLKYFIIQDRCPHTRDSTIQ	536
DSS_Rat_UMOD	VMLSTEAFLYVGTMLDGGDL ⁵³⁹ SRFVLLMTNCYATPSSNSTDPVKYFIIQDRCPHTEDTTIQ	539
* ***** .***** :*** :***** .* :***		
Human_UMOD	VVENGE ⁵⁹⁶ SSQGRFSVQMFRFAGNYDLVYLHCEVYLCDTMNEKCKPTCSG T FRFRSGSVIDQS	596
DSS_Rat_UMOD	VTENGE ⁵⁹⁹ SSQARFSIQMFRFAGNSDLVYLHCEVYLCDTMSEQCKPTCSGTRYRSGNFIDQT	599
* .***** .*** :***** ***** .* :***** :*** . .*** :		
Human_UMOD	RVLNLGPITRKGVQATVSR ⁶⁴⁰ AF-SSLGLLKVWLPLLLSATLTL T ⁶⁴⁰	640
DSS_Rat_UMOD	RVLNLGPITRQGVQASVSKAASSNLGFLSIWLLFLSATLTL ⁶⁴⁴ MVH	644
*****.* :***.* :* *.**.* :*.** * :***** . :		

* indicates amino acid identity (81%) between human and the rat. Probable human missense mutations (The Genomes Project et al., 2015) are shaded, which were curated from <https://www.ncbi.nlm.nih.gov/snp/> and as of April 23, 2020. Only those missense mutations with minor alleles that were observed at least 2 times (marked in red) in the tested populations are included with the validation status by 1000Genomes. Amino acids in blue indicate that the minor allele has been observed more than 10 times. The rat missense mutation has been experimentally confirmed and shaded in green. DSS, Dahl salt-sensitive rats.

Table Supplementary S7 (Table S7): Amino acid alignment and missense mutations in codons for BAG cochaperone 3 (BAG3) in humans and rats

Human_BAG3	MSAATHSE Y MQVASGNG--DRDPLPGWEIKIDPQTGWPFVVDHNSRTTTWNDPRVPSEG	58
DSS_Rat_Bag3	MSAATQSPVMQMASGNGASDRDPLPGWEIKIDPQTGWPFVVDHNSRTTTWNDPRVPPEG	60
*****.* :*. :*** ***** ***** ***** ***** ***** *		
Human_BAG3	PKET S SANGP S EGSRLPPARE G HPVYPQLRPGYIPIPVLHEGAENRQVHPFHVYPQPG	118
DSS_Rat_Bag3	PKETASSANGPSRDGSRLLPAREGHPIYPQLRPGYIPIPVHHEGSENQPHLFHAYSQPG	120
*** *****.* :*** ***** :***** ***** * * * . * *		
Human_BAG3	MQFRTEAAAAAPQRSQSPLRG-MPETTQPD K CGQVAAAAAQPASHGPERSQSPAAS	177
DSS_Rat_Bag3	VQFRTEAAAAAPQRSQSPLRGGVTETTQTDKCGQVPAAATAQPPTAHGPERSQSPAAS	180
:***** : ***** ***** * :***** :*****		
Human_BAG3	DCSSSSSSASLPSSGRSSLGSHQLPRGYISIPVIHEQNVT ²³⁷ RPAAQPSFHQAQKTHYPAQQ	237
DSS_Rat_Bag3	DCSSSSSSASLPSSGRSSLGSHQLPRGYIPIPV ²⁴⁰ IHEQNITRPAAQPSFHQAQKTHYPAQQ	240
***** ***** :***** :*****		
Human_BAG3	GEYQTHQPVYHKIQGDDWEP R PLRAASPF ²⁹⁷ RSSVQGASSREGSPARSSTPLHSPSPIRVHT	297
DSS_Rat_Bag3	GEYQPQQPVYHKIQGDDWEPRLRATSPFRSPVRGASSREGSPARSSTPLVHCPSP ³⁰⁰ PIRVHT	300
*** :***** .***** * :***** .* :*****		
Human_BAG3	VVDRPQQPMTHRETAPVSQPENKPESKPGPVGP E LPPGHIPIQVIRKEVDSKPVSQKPPP	357
DSS_Rat_Bag3	VVDRP-QPMTHREPPVTQPENKPESK P GLAG D LPPGHIPIQVIRREADSKPVSQKPPP	359
***** ***** **.* :***** .* :***** :* :*****		
Human_BAG3	PSEKVEVKVPPAPVPCPPSP G SAVPSSPKSVATEERAAPSTAPAEAT P PKPGAEAEAPP	417
DSS_Rat_Bag3	PAEKVEVKVSSAPIPCSPGPAPSAVPSSPKNVAAEPKAA ⁴¹⁹ SPAPAEAA L KSGDAEAP L	419
* :***** **.* :* *.***** .**.* :*** *****.* :* * :*****		
Human_BAG3	KHPGV ⁴⁷⁷ LKVEAILEKVQGLEQAVDNFEG K KTDKKYLMIEEYLTKE ⁴⁷⁷ LLALDSVDPEGRADVR	477
DSS_Rat_Bag3	KHPGV ⁴⁷⁹ LKVEAILEKVQGLEQAVDNFEGK K TDKKYLMIEEYLTKE ⁴⁷⁹ LLALDSVDPEGRADVR	479

Human_BAG3	QARRDGV ⁵³⁷ RKVQTILEKLEQKAIDVPQGVQVYELQPSNLEADQPLQAIMEMGAVAADKGKK	537
DSS_Rat_Bag3	QARRDGV ⁵³⁷ RKVQTILEKLEQKAIDVPQGVQVYELQPSNLEPEQPLQEIM--GAVAADKDKK	537
***** :***** ** *****.*		
Human_BAG3	NAGNAEDPHTETQQPEATAAATSNPSSMTDTPGNPAAP 575	575
DSS_Rat_Bag3	G-PENEDPQTESQGLEAKAATPPNPSSSTADSAGNPVAP 574	574
. : ***.* :** *.**.* :*** :* :***.*		

* indicates amino acid identity (89%) between human and the rat. Probable human missense mutations (The Genomes Project et al., 2015) are shaded, which were curated from <https://www.ncbi.nlm.nih.gov/snp/> and as of April 23, 2020. Amino acids in blue indicate that the minor allele has been observed more than 10 times. The rat missense mutation has been experimentally confirmed and shaded in green. Human 455K was associated in a GWAS with heart failure due to dilated cardiomyopathy (Eur Heart J. 2011;32:1065). DSS, Dahl salt-sensitive rats.

Table Supplementary S8 (Table S8): Amino acid alignment and missense mutations in codons for COBW domain containing (CBWD1) in humans and rats

Human_CBWD1	MLPFAVGSADDEEDPAEEDCP ¹ ELVP ¹ ETTTQSEEEKSGLGAKIPVTIITGYLGAGKTTLLN	60
DSS_Rat_Cbwd1	MLPAMKTVEA-EEEYAE ¹ DCPELV ¹ PIETKHQ ¹ EEENLDFI ¹ KIPVTIVTGYLGAGKTTLLN	59
	****: .: .: * : *****.:*:*: .: *****:*****	
Human_CBWD1	YILTEQHSKRVAIVILNEFGEGSALEKSLAVSQGGELYEEWLELRNGCLCCSVKDSGLRAI	120
DSS_Rat_Cbwd1	YILTEQHNRKIAVILNEFGEG ¹ AVEKSLAVSQGGELYEEWLELRNGCLCCSVKDNGLKAI	119
	*****.:*:*****.:*****:*****:*****.:*:**	
Human_CBWD1	ENLMQKKGKFDYILLETTGLADPGAVA ¹ SMFWVDAELGSDIYLDGIITIVDSKYGLKHLTE	180
DSS_Rat_Cbwd1	ENLMQKKGKFDYILLETTGLADPGAVASMFVDAELGSDIYLDGIITVDSKYGLKHLTE	179
	*****:*****:*****:*****:*****:*****:*****	
Human_CBWD1	EKPDGLINEAT ¹ QVALADAILINKTDLVPEEDVKKLRTTIRSINGLGQILETQRSRV ¹ DLS	240
DSS_Rat_Cbwd1	EKPDGLVNEATRQVALADMILINKTDLVSEELNKLRTTIRSINGLGK ¹ VLETQRSRTHLS	239
	*****:***** ***** **.:*:*****.:*****. .**	
Human_CBWD1	NVLDLHAFDSL ¹ SGISLQKKLQHVPGTQPHLDQSI ¹ VTITFEVPGNAKEEHLNMF ¹ IQNLLWE	300
DSS_Rat_Cbwd1	NILDLHAYDTLSG ¹ ISLQKKLQHVS-TAPHL ¹ DQSI ¹ VTVTFDVPGSAEEESLN ¹ VFIQNLLWE	298
	*:*****.:***** ***** * *****:*.**:*.*:** *:*****	
Human_CBWD1	KNVRNKDNHCMEVIRLKGLVSIKDKS ¹ QVIVQGVHEL ¹ YDLEETPVSWKDDTERTNRLVLL	360
DSS_Rat_Cbwd1	KNVKNKGRCMEVIRLKGLVSIKDKPQ ¹ QMI ¹ VQGIHEL ¹ ELESRVNWKDDAERACQLVFI	358
	:.:***** ***** **:*****:***:*.*****:*:.:**:	
Human_CBWD1	GR ¹ NLDKDILKQLFIATVTETEKQWTRFQEDQVCT-- 395	
DSS_Rat_Cbwd1	GKNLDKDILQQLFITAVAETKEQTAP-GQDGACPPH 394	
	*:*****:*****.:*:*:*: * : : * *	

* indicates amino acid identity (85%) between human and the rat. Probable human missense mutations (The Genomes Project et al., 2015) are shaded, which were curated from <https://www.ncbi.nlm.nih.gov/snp/> and as of April 23, 2020. Only those missense mutations with minor alleles that were observed at least 2 times (marked in red) in the tested populations are included with the validation status by 1000Genomes. Amino acids in blue indicate that the minor allele has been observed more than 10 times. The rat missense mutation has been experimentally confirmed and shaded in green. DSS, Dahl salt-sensitive rats.

Table Supplementary S9 (Table S9): Amino acid alignment and missense mutations in codons for dedicator of cytokinesis 8 (DOCK8) in humans and rats

Human_DOCK8	MATLPSAERRAFALKINRYSS ¹ EIRKQFTLPPNLGQYHRQSISTSGFPSLQLPQFYDPVE	60
DSS_Rat_Dock8	MATLPSAERRAFALKINRYSS ¹ EIRKQFTLPPNLGQYHRHSLSTSGFPSLQLPQLYEPVE	60
	*****:*****.:*****:*****.:*****:*****:*****	
Human_DOCK8	PV ¹ DFEGLLMTHLNSLDVQLAQELGDFTD ¹ DDLVDVFT ¹ EKECRTLQPSLPEEGVELDPHVRD	120
DSS_Rat_Dock8	PVDFEGLVMTHLNSLDAELAQELGDLTD ¹ DDLHVAF ¹ TPKECRTLQHS ¹ LPEEGVELDPHVRD	120
	*****.:*****.:*****:*****.*.***** *****	
Human_DOCK8	CVQTYIREWLIVNRKNQGSPEICGFKKTGSRKDFHKTLPKQTFESETLECSEPA ¹ AQAGPR	180
DSS_Rat_Dock8	CVQTYIREWLIVNRKNQGSPEFC ¹ SKTGSRRDFHKTLQKQTFESETLECSEPATQTGPR	180
	*****:*****.:*****:***** *****:*****.:**	
Human_DOCK8	H-LNVLCDVSGKGPVTACDFDLRSLQPD ¹ KRLLENLLQQVSAEDFEKQ ¹ N ¹ EEARR ¹ T ¹ NRQA ¹ ELF	239
DSS_Rat_Dock8	HRFNVLCDSVSGKGPITSCDFDLRSLQPD ¹ ERLENLLQ-LSAEDFEKEKEEARKTNRTAELF	239

	* :*****:*:*****:***** :*****:*****:*** **	
Human_DOCK8	ALYPSVDEEDAVEIRPVPECPKEHLGNRILVKLLTLKFEIEIEPLFASIALYDVKERKKI	299
DSS_Rat_Dock8	ALYPSVDEEDAVEIRPVPECPKEHLGNRILVKVLTlKFEIEIEPLFASIALYDVKERKKI *****:*****	299
Human_DOCK8	SENFHCDLNSDQFKGFLRAHTPSVAASSQARSASFVSVTYPSSDIYLVVKIEKVLQQGEIG	359
DSS_Rat_Dock8	SENFHCDLNSDQFKGFLRAHTPSVDPSSQARSASFVSVTYPSSDIYLVVKIEKVLQQGEIA *****	359
Human_DOCK8	DCAEPYTVIKESDGGKSKEKIEKLLQAESFCQRLGKYRMPPFAWAPISLSSFFVSTLER	419
DSS_Rat_Dock8	DCAEPYMIKESDGGKSKEKVEKLLQAESFCQRLGKYRMPPFAWAPISLASFFNVSTLER *****:*****:*****:*****:*****	419
Human_DOCK8	EVTDVDSVVGRSSVGERTLAQSRRLSERALSLEENGVGSNFKTSTLSVSSFFKQEGDRL	479
DSS_Rat_Dock8	ESTDLEPGAGNSVGERRSLQSRRPSERTLSFEENGVGSNFKTTTLATNIFFKQEGDRL * **: : .*.*****:***** **:*:*****:*: . . *****	479
Human_DOCK8	SDEDLFKFLADYKRSSSLQRRVKSIPGLRLLEISTAPEIINCCLTPEMLPVKPFPENRTR	539
DSS_Rat_Dock8	SDEDLFKFLADYKRSSSLQRRVKSIPGSLRLIAPAPDVMNCCLTPEMLPVKPFPENRTR ***** *****: **: : *****	539
Human_DOCK8	PHKEILEFPTREVYVPHTVYRNLLYVYPQRLNFNVKLASARNITIKIQFMCGEDASNAMP	599
DSS_Rat_Dock8	PHKEILEFPIREVYVPHTVYRNLLYVYPQRLNFANKLASARNITIKIQFMCGEDPSNAMP ***** *****:***** *****	599
Human_DOCK8	VIFGKSSGPEFLQEVYTAVTYHNKSPDFYEEVKIKLPAKLTVNHHLLFTFYHISCQQKQG	659
DSS_Rat_Dock8	VIFGKSSGPEFLQEVYTAITYHNKSPDFYEEVKIKLPAKLTVNHHLLFTFYHISCQQKQG *****:*****:*****:*****:*****:*****:*****	659
Human_DOCK8	ASVETLLGYSWLPILLNERLQTGSYCLPVALEKLPNYSMHSAEKVPLQNPPIKWAEGHK	719
DSS_Rat_Dock8	ASGESLLGYSWLPILLNERLQTGSYCLPVALEKLPNYSIHSAEKVPLQNPPIKWAEGHK ** *:*****:*****:*****:*****:*****:*****	719
Human_DOCK8	GVFNIEVQAVSSVHTQDNHLEKFFTLCHSLESQVTFPIRVLDQKISEMALEHELKLSIIC	779
DSS_Rat_Dock8	GVFNIEVQAVSSVHTQDNHLEKFFTLCHSLESQVTFPIRVLDQKITENTLEHELKLSIIC *****:*****:*****	779
Human_DOCK8	LNSSRLEPLVLFLHLVLDKLFQLSVQPMVIAGQTANFSQFAFESVVAIANSLHNSKDLSK	839
DSS_Rat_Dock8	LNSSRLEPLVLFLHLVLDKLFQLSVQPMVIAGQTANFSQFAFESVVAIANSLHNSKDLRK ***** *	839
Human_DOCK8	DQHGRNCLLASVYHYVFRLEPVQRDVPKSGAPTALLDPRSHTYGRTSAAAVSSKLLQAR	899
DSS_Rat_Dock8	DQHGRNCLLASVYHYVFRLEPDLHRDAPKSGGPTAVVDPDPRYHTYGRTSAAAVSSKLMQAR *****:*.***.***: *****:***	899
Human_DOCK8	VMSSSNPDLAGTHSAADEEVKNIMSSKIADRNCRMSYCSGSSDAPSSPAAPRPASKKH	959
DSS_Rat_Dock8	VMSSSNPDLAGTHCAADEEVKNIMSSKIADRNCRMSYCSGNSDVPGSTAAPRPVSKKH ***** .***** .*. * ***** .***	959
Human_DOCK8	FHEELALQMVVSTGMVRETVEFKYAWFFFELLVKMSAQVHNMDKRDSEFRTRFSDRFMDD	1019
DSS_Rat_Dock8	FHEELALQMVVSTGLVRETVEFKYAWFFFELLVKMSAQVHNLDKRDSEFRTRFSDRFKDD *****:*****:***:***** **	1019
Human_DOCK8	ITTVNVVTSEIAALLVKPQKENEQAEKMNISLAFFLYDLLSLMDRGVFVNLIRHYCSQL	1079
DSS_Rat_Dock8	ITTVNVVTSEIAALLVKPQKESEQAEKINISLAFFLYDLLSIMDRGFVNLIKHCTQL ***** .*****:*****:*****:***: **	1079
Human_DOCK8	SAKLSNLPPTLISMRLFLRLCSHEHYLNLNLFMNADTAPTSPCPSISSQNSSSCSSFQ	1139
DSS_Rat_Dock8	SAKLNTLPPTLISMRLFLRLCSHEHYLNLNLFMNPDAPASPCPSISSQNSSSCSSFQ ****.*****:*** *****:*****	1139
Human_DOCK8	DQKIASMFDLTSEYRQQHFLTGLLFTELAAALDAEGEGISKVQRKAVSAIHSLSSHDLD	1199
DSS_Rat_Dock8	DQKIASMFDLTPEYRQQHFLTGLLFTELAVALDAEGDGISRVQRKAVSAIHSLSSHDLD ***** *****:***:*****	1199
Human_DOCK8	PRCVKPEVKVKIAALYLPVGIILDALPQLCDFTVADTRRYRTSGSDEEQEGAGAINQNV	1259
DSS_Rat_Dock8	PRCLKPEVKVKIAALYLPVGIILDALPQLYDFTDARSGRSRAGSYEQDVANGINQNV ***:***** ** *: * *:*** **: *.*****	1259
Human_DOCK8	ALAIAGNNFNKLTSGIVLSSLPYKQYNMLNADTTRNLMICFLWIMKNADQSLIRKWIADL	1319
DSS_Rat_Dock8	ALAIAGNHFNKLTSGAMLSSLPYKQYNMLNADTTRHLMVCFLWIMKNADQSLIRKWIADL *****:***** :*****:***:*****	1319
Human_DOCK8	PSTQLNRILDLLFICVLCFEYKKGQSSDKVSTQVLQKSRDVKARLEEALLRGEGARGEMM	1379
DSS_Rat_Dock8	PSMQLNRILDLLFICVSCFEYKKGQSSDKVSNQVLQKSRDVKARLEEALLRGEGARGEMM	1379

[illegible]

Table Supplementary S10 (Table S10): Amino acid alignment and missense mutations in codons for KN motif and ankyrin repeat domains 1 (KANK1) in humans and rats

DSS_Rat_Kank1	PPAPLETSPPTFAISENRQLLPPPSPQLPRHNLHVTKTLMETRRRLQEQRVTMQMAPGEFR ** ***** * :.: *****;*****;****;*****	180
Human_KANK1	RPLRASFSGMGTTSSLSFVFGSGNHNPAKQLQNGYQGNGDYGSYAPAAPTSSMGSSIR	240
DSS_Rat_Kank1	RPLRASFSGMGSTSSLPFSFMGSGNHSSAMHQLQNGYQGNGDYSSYPVAVPTTSSMGSSVR *****;*****;*****. * *****.*. *. *****;*	240
Human_KANK1	HSPLSSGISTPVTNVSPMHLQHIREQMAIALKRLKELEEQVRTIPVLQVKISVLQEEKRQ	300
DSS_Rat_Kank1	HSPLSSGISTPVTNVSPMHLQHIREQMAIALKRLKELEEQVRTIPVLQVKISVLQEEKRQ *****	300
Human_KANK1	LVSQ LKNQRAASQINVC GVRKRSYSAGNASQLEQLSRARRSGGELYIDYEEEEEMETVEQS	360
DSS_Rat_Kank1	LASQ LKNQRAASQNEACGV RKR SYSAGNASQLELLSRARRGGGELYIDYEEEEESVEQS *. ***** .: ***** *****. *****;***	360
Human_KANK1	TQRIKEFRQLTADMQA LEQKI QDSSCEASSELENRENGECR----SVAVGAEENMNDIVVY	415
DSS_Rat_Kank1	TQRIREFRQLTADMQA LEQKI QDSSCEATPELRENGQCASRERKS VAVGSDENMNDIVVY ****;*****;*****: *****;* *****.;*****	420
Human_KANK1	HGRSRCKDAAVGT LV MRNCGVSVTEAMLGVMTEADKEI ELQQQTIE SLKEKIYRLEVQ	475
DSS_Rat_Kank1	HRDFRSRKDTAVGT VTETRNFGISVTEAM LGVITEADKEI ELQQQTIEALKEKIYRLEVQ **.* ** *:****;. * ** *:*****;*****;*****	480
Human_KANK1	LRETTHDREM TKLKQELQAAGSRKKVDKATMAQPLVF SKVVEAVVQTRDQMVGSHMDLV D	535
DSS_Rat_Kank1	LKETTHDREM TKLKQELQAAGSRKKVDKA IMAQPLVFSKLVEALVPTREQMVGSHVDT ID *: ***** *****;***;* **:*****;*. *	540
Human_KANK1	TCVGT SVETNSVGIS CQPECKNKVGP ELP MNWVI KERVEMHDCAGR SVMCDKSVSV	595
DSS_Rat_Kank1	SCVGT SVQTSSVGT SCHPDRKNQVVGPELP MNWVV KERVGTHDCVGRSVETCNRSVGV :*****;*. *** *:*: *:*****;***** ****.***** *:**. *	600
Human_KANK1	EVSVCETGSNT EESV DL TLLKT NLNL KEVRSIGCGDCSV DVTVCSPEK CASRGVN TEAV	655
DSS_Rat_Kank1	EVSVCETGSNT EASGSDL TLLKT NLNL KDVRSIGCGDCSVDVIVCLPKECTSRSMNTEAV ***** * .*****;***** * * *****;*. :*****	660
Human_KANK1	SQVEAAVM AV P TADQDTSTDLEQVHQFTNTETATLIESCTNTCLSTLDKQTSTQT VETR	715
DSS_Rat_Kank1	GQGEAAVM AVPH TT DQHTSTNL ERVDQGT NTEVTTLVESC TNTLLSTLDKQTSTQN VMER . * *****;*. *. *. *. *. * **. .: *:***** *****;*. *	720
Human_KANK1	TVAVAGEGR VKDINSSTKTRS IGVTLLSGHSGFDRPSAVKTKESGVGININDNYLVGLK	775
DSS_Rat_Kank1	TVAIGEGRV RDINPSTK TRSVGV GTVLSGSSDFDKPCA VTKESGVGINIH DNYLVGLK ***;*****;*** *****;****.*** *. *. *. *****;*****	780
Human_KANK1	MRTIACGPPQLTVGLTASRRSVGVGD DPVGESLENP-QQPAPLGMMTG LDHYIERIQKLL	834
DSS_Rat_Kank1	MRTIACGPPQLTVGLIGSRRSVGVGN EPVGD LLEDPLQPQVSGMMTG LDHYIERVQKLL *****;*****.*****;*****:***** * * *****;***	840
Human_KANK1	AEQQTLLAENYSELAEAFGE PHSQMGS LNSQLISTLSSINSVMKSA STEELRNPDFQKTS	894
DSS_Rat_Kank1	AEQQTLLAENYSELAEAFGE PHSIGSLNSQLISTLSSINSVMKSA STEELRNPDFQKSS *****;*****;*****;*****;*****;*****;*****;*****;*	900
Human_KANK1	LGKIT NYLGYTCKCGGLQSG SPLSSQTSQPEQEVGTSE GKPISSLDAFPQTQEGT LSPVN	954
DSS_Rat_Kank1	LKGIAGNHLE CTCKCGLRSGGLV NVQTSQPEVETTETGKR--GCEQFLTQGN TLPPVN ****;*. *: *****;*. .: ***** *. *:*** .: * ** .* **	958
Human_KANK1	LTDDQIAAGLYACTNNESTLKSIMKKKDGNKDSNGAKKNLQFVGINGGYETTSSDSSSD	1014
DSS_Rat_Kank1	LTDDQIATGLVCPNNENTLKSIMKSDGNKDSNGAKKNLQFVGNGGYETTSSDSSSG *****;***.* ***.*****.*****;*. *****;	1018
Human_KANK1	ESSSESDEDCDV IEYPLEEEE---EEDDEDTRGMAEGHHAVN EGLKSARVEDEMQVQ	1070
DSS_Rat_Kank1	GSSSESDEDCDTNGY PPEEEEEEEEEEDHDTRGMAEGHHAVNI EGFSARVEDEVQVP *****. ** **** *****.*****;*****;*****;*	1078
Human_KANK1	ECEPEKVEIRERYELSEKMLSACNLKNTINDPKALT SKDMRFCLNTLQHEWF RVSSQKS	1130
DSS_Rat_Kank1	ECEPEKEEIRERYELSEKMLSACSLKYNI ND PKALASKDMRICLNTLQHEWFRVSSQKS ***** *****;***.*****;*****;*****;*****	1138
Human_KANK1	AIPAMVG DYIAAFE AISPDVLR YVINLA DGNGTALHYSVSHSNFEIVKLLLDADV CNVD	1190
DSS_Rat_Kank1	AVPAMVG DYIAAFE AVSPDLRYII NMADGNGTALHYSVSHSNFQIVKLLLDADV CNVD *;*****;*****;*****;*. *****;*****;*****;*****	1198
Human_KANK1	HQNKAGYTPIMLAALA AVEAEKDMRIVEELFCGCDVNAKASQAGQTALMLAVSHGRIDMV	1250
DSS_Rat_Kank1	HQNKAGYTPIMLAALA AVEAEKDMQVVEELFSCGCDVNAKASQAGQTALMLAVSHGRIDMV *****;*****.*****.*****;*****;*****;*****	1258
Human_KANK1	KGLLACGADV NIQDDEGSTALMCASEHG HVEIVKLLLAQPGCNGHLEDND GSTALSIALE	1314

DSS_Rat_Kank1	KGLLACGADVNIQDDEGSTALMCASEHGHVEIVKLLLAQPGC	GHLEDNDGSTALSIALE	1318

Human_KANK1	AGHKDIAVLLYAHVNFAKAQSPGTPRLGRKTSPGPTHRGSFD		1352
DSS_Rat_Kank1	AGHKDIAVLLYAHNLNFSKAQSPSTPRLGRKTSPGPTHRGSFD		1360
	*****:*.*****		

* indicates amino acid identity (87%) between human and the rat. Probable human missense mutations (The Genomes Project et al., 2015) are shaded, which were curated from <https://www.ncbi.nlm.nih.gov/snp/> and as of April 23, 2020. Only those missense mutations with minor alleles that were observed at least 2 times (marked in red) in the tested populations are included with the validation status by 1000Genomes. Amino acids in blue indicate that the minor allele has been observed more than 10 times. The rat missense mutation has been experimentally confirmed and shaded in green. DSS, Dahl salt-sensitive rats.

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