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REVIEW SERIES

Mapping genetic determinants of kidney damage in rat models

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During the last two decades, significant progress in our understanding of the development of kidney diseases has been achieved by unravelling the mechanisms underlying rare familial forms of human kidney diseases. Due to the genetic heterogeneity in human populations and the complex multifactorial pathogenesis of the disease phenotypes, the dissection of the genetic basis of common chronic kidney diseases (CKD) remains a difficult task. In this regard, several inbred rat models provide valuable complementary tools to uncover the genetic basis of complex renal disease phenotypes that are related to common forms of CKD. In this review, data obtained in nine experimental rat models, including the Buffalo (BUF), Dahl salt-sensitive (SS), Fawn-hooded hypertensive (FHH), Goto-Kakizaki (GK), Lyon hypertensive (LH), Munich Wistar Frömter (MWF), Sabra hypertension-prone (SBH), spontaneously hypertensive rat (SHR) and stroke-prone spontaneously hypertensive rat (SHRSP) inbred strains, that contributed to the genetic dissection of renal disease phenotypes are presented. In this panel of inbred strains, a large number of quantitative trait loci (QTL) linked to albuminuria/proteinuria and other functional or structural kidney abnormalities could be identified by QTL mapping analysis and follow-up studies including consomic and congenic rat lines. The comprehensive exploitation of the genotype–renal phenotype associations that are inherited in this panel of rat strains is suitable for making a significant contribution to the development of an integrated approach to the systems genetics of common CKD.
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INTRODUCTION

Common forms of chronic kidney diseases (CKD) represent complex disease phenotypes that are influenced by both environmental and genetic factors.[1–5] Both arterial hypertension and type-2 diabetes mellitus are major contributors to complex CKD, which has a high prevalence in the general human population worldwide affecting ~11–15% of individuals in Europe and United States.[6–9] CKD represents as expected a major risk factor for the progression to end-stage renal disease but associates also with an increased risk of cardiovascular morbidity and mortality.[10,11] In addition to the assessment of impaired renal function or glomerular filtration rate, urinary albumin excretion rate (albuminuria) represents another important clinical marker for the evaluation of CKD and cardiovascular risk of patients.[10–15] These renal disease phenotypes are also inherited in several inbred rat strains many of which are hypertensive.[16] During the last decades, genetic mapping studies by genome-wide linkage analysis followed by fine mapping of selected quantitative trait loci (QTL) for renal disease phenotypes were reported. Subsequently, studies in consomic and congenic rats were performed to further unravel the genetics of kidney injury in inbred rat strains. For QTL confirmation, consomic strains were generated by transfer of an entire chromosome carrying a QTL from a donor strain into the disease background of a recipient strain or vice versa.[17] For QTL fine mapping analysis, congenic or subcongenic strains were established by transfer of chromosomal fragments of different length from the donor to the recipient background or vice versa.[16,17]

The aim of this report is to review the current status of genetic mapping studies of genetic determinants of kidney damage in these inbred rat models.

BUFFALO RAT

Strain breeding

The proteinuria-prone Buffalo/Mna (BUF) inbred rat strain was derived from random bred BUF rats, and established at Nagoya University in Japan.[18,19] This inbred strain demonstrated spontaneous thymomas.[19–21]

Strain characteristics

The normotensive[22] BUF rat strain develops spontaneous progressive proteinuria[23–25] in the nephrotic range, that is, >150 mg per 24 h,[26] hypoproteinemia,[23] abnormal lipid metabolism,[23] structural renal lesions such as focal and segmental glomerulosclerosis (FSGS) and glomerular epithelial cell alterations with foot process effacement later in life.[22,23,25,27–29] Both proteinuria and FSGS are not linked to the genetic susceptibility to develop spontaneous thymomas[21,25,27,30,31]

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and related immune disorder phenotypes.[32,33] Furthermore, BUF rats show muscle atrophy, fatigability and weakness.[34,35]

Cosegregation and linkage analyses

Linkage analysis in a male (BUF × Wistar Kyoto (WKY)/NCrj) F1 × BUF backcross population revealed significant linkage only to one locus, that is, the QTL *Pur1* (Proteinuria QTL 1) on rat chromosome (RNO)13 linked to the development of proteinuria (Tables 1 and 5).[24] Interestingly, this QTL explained about 39% of the total variance of proteinuria in the backcross population.[24] Further, fine mapping of *Pur1* by linkage analysis, physical mapping and single-nucleotide polymorphism analysis narrowed the QTL to a 7.8-Mb long region containing 38 genes of which 25 remained potential candidate genes for proteinuria.[19] Subsequently, in *Arp3* (actin-related protein 3) a missense mutation ($^{L}111^{F}$ substitution) was found causing actin assembly abnormalities in podocytes (Table 3).[19] This mutation was related to both proteinuria and FSGS development in the BUF rat.[19] No consomic or congenic studies were reported.

DAHL RAT

Strain breeding

Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rat strains were originally established as outbred strains from Sprague-Dawley rats by Lewis K Dahl.[36] DS and DR rats were selected for contrasting blood pressure (BP) values in response to high dietary salt intake (8% NaCl).[16,37] The inbred Dahl rat strains Dahl salt-sensitive (SS/Jr) and Dahl salt-resistant (SR/Jr) were derived from outbred DS and DR rats by Rapp.[16]

Strain characteristics

SS/Jr rats are characterized by salt-sensitive hypertension,[16,38] progressive proteinuria in response to high-salt diet and kidney damage, which is associated with glomerular, tubulointerstitial and vascular damage.[16,39–52] Interestingly, SS/Jr develops early onset spontaneous albuminuria at 4 weeks of age already when fed a normal/low-salt diet before ultrastructural glomerular changes[53] such as segmental loss of podocyte foot processes[43] are observed. However, the progression of hypertension and renal damage is attenuated under normal/low-sodium compared with high-sodium diet in aging rats.[16,38,43,48,53,54] The magnitude of albuminuria is not only enhanced by high-salt intake but also modified by the composition of dietary protein intake.[55,56] In addition, the rats develop left ventricular hypertrophy and fibrosis,[47,49,51,57] hyperlipidemia[46,51] and insulin resistance.[58–60]

Cosegregation and linkage analyses

Different studies addressed the genetics of albuminuria in SS rats under either normal/low-salt or high-salt diet. Poyan Mehr analyzed the genetic basis of early onset albuminuria on low-salt (0.2% NaCl) diet in SS rats by genome-wide QTL mapping analysis of albuminuria at 8 weeks of age in a large cohort of 539 (SS_{Fub} × spontaneously hypertensive rat $(SHR)_{Fub}$) F2 progeny.[53] Seven suggestive or significant UAE QTLs on RNO2, RNO6, RNO8, RNO9, RNO10, RNO11 and RNO19 accounting together for 34% of the overall variance of albuminuria were identified (Tables 1 and 5).[53] It was shown that homozygosity of two albuminuria increasing alleles for at least six QTLs was necessary to generate a considerable increase in UAE in young F2 rats.[53]

Garrett *et al.*[54] identified in a backcross population of 276 male rats derived from *F1*(Dahl SS/Jr (S) × SHR/NHsd) × S under low salt (0.3% NaCl) 10 albuminuria and/or proteinuria QTL on RNO1–RNO2, RNO6 (QTL1 + QTL2), RNO8–RNO11, RNO13 and RNO19, most of which colocalized with QTL for structural kidney lesion phenotypes (Tables 1 and 5). As expected, most of the S alleles were associated with increased albumin or protein excretion rates, although alleles on RN06 (QTL1) and RNO11 were also linked to decreased albumin excretion rates.[54] The albuminuria RNO2-QTL was involved in multiple interactions with albuminuria QTL on other chromosomes.[54] Subsequently, the authors confirmed in an independent backcross population fed low salt (0.3% NaCl) all previously identified low-salt albuminuria QTL[54] except the RNO6-QTL1 and the QTL on RNO10 (Table 1).[61] Thus, taken together six common albuminuria QTLs on RNO2, RNO6, RNO8, RNO9, RNO11 and RNO19 were identified in all three studies, respectively (Tables 1 and 5).

Subsequently, further studies analyzed the genetic influence on renal damage in response to high-salt diet in the SS rat. One study again in a backcross between SS and SHR rats demonstrated that the albuminuria/proteinuria QTL on RNO2, RNO11 and RNO19 that were detected under low-salt exposure were not detectable under high-salt diet (Table 1).[61] The authors hypothesized that SHR alleles on RNO11 may mediate preglomerular vasoconstriction and hence, protect against renal damage in response to an increased blood pressure after high salt in backcross animals.[61] Four of the albuminuria/proteinuria QTL reported in this study on RNO6, RNO8, RNO9 and RNO19 were also confirmed in a similar cross.[48] In the latter study, the effect of high-salt intake (4% NaCl) was analyzed in an F2 cross derived from SS/Rkb × SHR/Rkb and led to the identification of overall six albuminuria/proteinuria QTLs on RNO3, RNO6 (2 QTL), RNO8, RNO9 and RNO19 (Tables 1 and 5).[48] Moreover, the authors detected also QTL linked to structural kidney injury phenotypes, for example, renal interstitial fibrosis, tubulointerstitial inflammation and renal microangiopathy on RNO20, RNO3 and RNO5, respectively (Tables 1 and 5).[48] Of interest, the SHR allele was associated with a more severe phenotype at the tubulointerstitial inflammation and microangiopathy QTL.[48]

Moreno *et al.*[62] identified in a female-specific linkage analysis of (SS/JrHsdMcwi × Brown Norway (BN)/SsNHsdMcwi) F2 animals 126 QTL for 96 cardiovascular, renal and other traits in response to graduated NaCl intake. A QTL on RNO2 was found to be associated with proteinuria and focal glomerulosclerosis and a QTL on RNO11 with proteinuria and glomerular injury (Tables 1 and 5).

Consomic/congenic studies

Different consomic and congenic/subcongenic studies between SS and SHR or SS and BN were performed to unravel the genetics of kidney damages in SS rats.

SS and SHR. Wendt *et al.*[49] analyzed the effect of replacement of the albuminuria/proteinuria QTL on SS-RNO19 previously described by Siegel *et al.*[48] Transfer of SHR-RNO19 into SS revealed in consomic $SS\text{-}19^{SHR}$ a protective effect of RNO19 on albuminuria and proteinuria in both sexes under both low- and high-salt diet (Table 2).[49]

In different congenic and subcongenic studies, the phenotypic effects of proteinuria and albuminuria QTL that were originally detected under low- and/or high-salt diet on RNO2, RNO6, RNO8, RNO9, RNO11 and RNO13[54,61] were confirmed by transfer from SHR into the SS strain (Table 2).[52,63,64] The RNO2-QTL demonstrated a major influence on proteinuria/albuminuria and glomerular, tubular and interstitial phenotypes, and fibrosis without influencing BP.[61,65] Recombinant progeny testing refined this QTL on

Table 1 Renal disease QTL identified in genome-wide linkage analyses of genetic rat models

Cross	*Ref.*	*Sex*	*Treatment*	*Week*	*Phenotype*	*QTL on RNO*
BUF × WKY BC	19,24	m	Normal diet	20–60	Proteinuria	**13**
FHH × ACI BC	77	m	Normal diet	36	Proteinuria	**1** (Rf-1), 1 (Rf-2)
				36	Focal glomerulosclerosis	**1** (Rf-1), **1** (Rf-2)
FHH × ACI F2	90	m	Normal diet, Nx	14	Albuminuria	**1** (Rf-1), **1** (Rf-2), **1** (Bpfh1), **3**, 14, **17**
				14	Proteinuria	**1** (Rf-1), **1** (Rf-2), **1** (Bpfh1), **3**, 14, 17
				14	Focal glomerulosclerosis	**1** (Rf-1), 1 (Rf-2), 3, 14
FHH.1^{BN} × FHH F2	91	f	0.4% NaCl	20	Renal blood flow autoregulation	**1**
GK × BN F2	114	m	1% NaCl	12, 24, 36, 48	Proteinuria	**5**, **7**
				48	Glomerulosclerosis	5, 7
				48	Tubular sclerosis	5, 7
				12, 24, 36, 48	Diabetes phenotypes	**1**, **4**, **5**, **10**
LH × LN F2	124,126	m	0.3% NaCl	29–31	Creatinine levels	1, 2, 17
					Kidney weight	**1,** 2, 3, 10, **17**
MWF × Lew BC	141	m	0.2% NaCl	8, 14, 24	Albuminuria	**1** (QTL1), 6 (QTL1), **12**, **17**
				8, 14, 24	Proteinuria	1 (QTL1), **17**
				24	Superficial glomeruli	X
				24	Surface glomeruli	1, 13
MWF × SHR BC	142	m	0.2% NaCl	8, 14, 24	Albuminuria	**1** (QTL2), 4, **6** (QTL2), 7, **8**, **9**, 15, X
				8, 14, 24	Proteinuria	**1** (QTL2), **6**, **8**, 15
				24	Renal interstitial fibrosis	6
				24	Superficial glomeruli	2, **6**, 7, 9
				24	Surface glomeruli	**6**
SBH × SBN F2	152	m	0.2% NaCl, Nx	12, 20, 24, 28, 32	Proteinuria	**2,** 3, **17, 20**
SBH × SBN BC	150	m	0.2% NaCl, Nx	16	Proteinuria	**2**, **6**, **9**, **20**
		f	0.2% NaCl, Nx	20	Proteinuria	**11**, **13**, **20**
SHR-A3 × SHR-B2 F2	168	m	0.2% NaCl	25	Immunoglobulin G subclasses associated with albuminuria	6
SHRSP × SHR F2	176	m, f	1% NaCl	10	Renal vascular/parenchymal lesions	1 (**QTL1** + 2), 4, **10**, **16**
SS × SHR F2	53	m	0.2% NaCl	14	Albuminuria	**2**, **6** (QTL2), 8, **9**, 10, 11, **19**
SS × SHR BC	54	m	0.3% NaCl	8, 12, 16	Albuminuria	**1**, **2**, **6** (QTL2), **8**, **9**, 10, **11**, **13**, **19**
				8, 12, 16	Proteinuria	**1**, **2**, **6** (QTL1 + 2), **8**, 9, **10**, **11**, 19
				16	Kidney lesion grade	**2**, 6, 8, 11, 13, 19
SS × SHR F2	61	m	2% NaCl	8, 12, 16	Albuminuria	**1**, 6 (QTL2), **8**, 9, 13
				8, 12, 16	Proteinuria	**1**, 6 (QTL2), **8**, **9**
				16	Kidney lesion grade	1, 2, **8**, 9, 13
SS × SHR F2	48	m	4% NaCl	14	Albuminuria	**6** (QTL**1** + 2), 8, 9, **19**
				14	Proteinuria	3, **6** (QTL1), **19**
				14	Renal interstitial fibrosis	20
				14	Tubulointerstitial inflammation grading	3
				14	Microangiopathy	5
SS × BN F2	62	f	0.4/0.1/8% NaCl	12	Proteinuria	2, 11
				12	Focal glomerulosclerosis	**2**
				12	Glomerular injury	11

Abbreviations: ACI, August × Copenhagen Irish; BC, backcross; BN, Brown Norway; BUF, Buffalo; f, females; FHH, Fawn-hooded hypertensive; GK, Goto-Kakizaki; Lew, Lewis; LH, Lyon hypertensive; LN, Lyon normotensive; m, males; MWF, Munich Wistar Frömter; QTL, quantitative trait loci; Ref., reference; RNO, rat chromosome; SBH, Sabra hypertension prone; SBN, Sabra hypertension resistant; SHR, spontaneously hypertensive rat; SHRSP, spontaneously hypertensive rat, stroke prone; SS, Dahl salt-sensitive; WKY, Wistar-Kyoto.
Statistical thresholds for significance in linkage analysis were used as recommended by Lander and Kruglyak[205] and maximal logarithm of odds (LOD) score values in BC or F2 populations are given in bold when indicative for significant linkage.

RNO2 to an interval, which spans 1.5 cM or ~5.0 Mb containing 64 known and/or predicted genes (Table 3).[65] Among these candidates, *Sfrp2* (secreted frizzled-related protein 2) and *Wnt2b* (wingless-type MMTV integration site family, member 2B) represent members of the Wnt/β-catenin signalling pathway and are of interest because they are involved in renal fibrosis. Moreover, *Cct3* (chaperonin containing TCP1, subunit 3) as another candidate in this interval seems to affect cytoskeleton integrity (Table 3).[65]

In a reciprocal approach by transfer of SS-RNO8 or SS-RNO13 into the renal-protective SHR background, no significant changes were observed in the derived congenic strains SHR.S(8) and SHR.S(13) for proteinuria, glomerular, tubular or interstitial injury.[52]

SS and BN. In a complete chromosome, substitution panel involving SS and BN rat designate as SS(/Mwcwi)-xBN(/SSNHsdMcwi) consomics each BN chromosome was transferred into the SS

Table 2 Confirmed renal disease QTL of genetic rat models by consomic and/or congenic studies

Cross/reference consomics or congenics	*Treatment*	*Phenotype*	*Confirmed QTL on RNO*
FHH × ACI[77,90–96,98,101,103,104]			
ACI.FHH-(*D1Rat74-D1Rat90*) or Rf-1A	8.0% NaCl/	Proteinuria	1, 3
ACI.FHH-(*D1Rat298-D1Rat90*) or Rf-1A	L-NAME/	Albuminuria	1, 3
ACI.FHH-*D1Mit34/Rat156* or ACI.FHH-Rf1B	Nx	Glomerular damage	1, 3
ACI.FHH-(*D1Rat324-D1Rat156*) or Rf-1B		Autoregulation of renal blood flow	1
ACI.FHH-(*D1Rat384-D1Rat156*) or Rf-1B		Susceptibility to renal failure	1 + 3, 1 + 14
ACI.FHH-(*D3Wox2-D3Rat59*) or Rf-3			
Rf-3_b (D3Got102-D3Got121)			
ACI.FHH-(*D1Rat475-D1Rat90*)/(*D3Rat84-D3Rat59*) or Rf-1A + 3			
ACI.FHH-(*D1Mit18-D1Rat90*)/(*D14Mit11-D14Rat33*/*D14Rat65-D14Rat90*) or ACI.FHH-Rf-1 + 4			
ACI.FHH-(*D1Mit18-D1Rat90*)/(*D14Rat98-D14Hmgc18*)/Mcwi or Rf-1a + 4_a			
ACI.FHH-(*D1Mit18-D1Rat90*)/(*D3Rat84-D3Rat59*)/(*D14Mit11-D14Rat33*/*D14Rat65-D14Rat90*) or Rf-1 + 3 + 4			
ACI.FHH-(*D1Mit18-D1Rat90*)/(*D3Rat6-D3Got149*)/(*D14Mit11-D14Rat33*/*D14Rat65-D14Rat90*) or Rf-1 + 3 + 4_a			
ACI.FHH-(*D1Mit18-D1Rat90*)/(*D3Got102-D3Got149*)/(*D14Mit11-D14Rat33*/*D14Rat65-D14Rat90*) or Rf-1 + 3 + 4_b			
ACI.FHH-(*D1Mit18-D1Mit8*)/(*D14Mit11-D14Hmgc14b*/*D14Rat65-D14Rat90*) or Rf-1B + 1			
FHH × BN[66,102,103,104]			
FHH.1^{BN}AR^{+}	Normal salt or 8.0%	Albuminuria	1, 15, 16, 18
FHH-1^{BN}	NaCl L-NAME	Proteinuria	1, 14, 15, 16
FHH-15^{BN}		Glomerular injury	1, 15, 16, 18
FHH-16^{BN}		Blocked medullary tubules (males)	15, 16
FHH-18^{BN}		Autoregulation of renal blood flow	1
FHH-20^{BN}			
FHH.BN-Rab38			
LH × BN[127]			
LH-13^{BN}	0.3% NaCl	Proteinuria (may depend on higher BP)	13
BN-13^{LH}			
MWF × SHR[138–140,142–144]			
MWF-6^{SHR}	0.2% NaCl	Albuminuria	6, 8, 6 + 8
MWF-8^{SHR}		Total nephron number	6, 6 + 8
MWF-6^{SHR}8^{SHR}		Renal interstitial fibrosis	6, 8 (females)
SHR-6^{MWF}		Glomerulosclerosis	6, 6 + 8
SHR-8^{MWF}		Tubulointerstitial damage	6, 8
		Podocyte alterations	6, 8, 6 + 8
SBH × SBN[150,152]			
SBH.1^{SBN}	Normal diet	Proteinuria	1, 2, 17, 20
SBH.2^{SBN}			
SBH.17^{SBN}			
SBH.20^{SBN}			
SBH.X^{SBN}			
SHR × BN[170]			
SHR.BN-D1Mit3/Igf2	1%NaCl/0.2% KCl, DOCA	Renal damage such as proteinuria and glomerular injury	1
SHRSP × SHR[176,185]			
SHRSPwch1.0	1% NaCl, stroke-permissive diet	Albuminuria	1
SHRSP.WKY-(*D1Rat44-D1Arb21*) or SHRSPwch1.5		Glomerulosclerosis	1
SHRSP.WKY-(*Apbb1-D1Arb21*) or SHRSPwch1.8			
SHRSP.WKY-(*D1Mgh5-D1Rat44*) or SHRSPwch1.9			
SHRSP.WKY-(*D1Mgh5-D1Wox29*) or SHRSPwch1.11			

Table 2 (Continued)

Cross/reference consomics or congenics	*Treatment*	*Phenotype*	*Confirmed QTL on RNO*
SS × *SHR*[52,54,61,63–65]			
S.SHR(2)	0.3% or 2% NaCl	Proteinuria/albuminuria	2, 6 (QTL2), 8, 9, 13
S.SHR(6)		Glomerular injury	2, 8
S.SHR(8)		Tubular and interstitial injury	2, 8, 13
S.SHR(9) × 4A		Fibrosis	2, 8, 13
S.SHR(9) × 2B			
S.SHR(11)			
S.SHR(13)			
SS × *SHR*[48,49,53]			
SS-19^{SHR}	0.2% or	Proteinuria	19
	4% NaCl	Albuminuria	19
SS × *BN*[55,62,66–69,73,102]			
SS- × BN	0.4% or	Proteinuria/albuminuria (m)	1, 5–8, 11, 13, 16, 18, Y
	4% or	Proteinuria/albuminuria (w)	1–2, 4–14, 16, 18–20
	8% NaCl	Structural glomerular injury	1
		Medullary interstitial fibrosis	13
		Tubular necrosis	13
		Glomerulosclerosis	13

Abbreviations: ACI, August × Copenhagen Irish; AR, autoregulation; BP, blood pressure; BN, Brown Norway; BUF, Buffalo; DOCA, deoxycorticosterone acetate; f, female; FHH, Fawn-hooded hypertensive; LH, Lyon hypertensive; L-NAME, N$^{\omega}$-nitro-L-arginine methyl ester; m, males; MWF, Munich Wistar Frömter; QTL, quantitative trait loci; RNO, rat chromosome; SBH, Sabra hypertension prone; SBN, Sabra hypertension resistant; SHR, spontaneously hypertensive rat; SHRSP, spontaneously hypertensive rat, stroke prone; SS, Dahl salt-sensitive; WKY, Wistar-Kyoto.

background, respectively.[66] For consomic studies, the animals were fed diets with different salt content, for example, normal (0.4%) or high-salt diets (4% or 8% NaCl) and protein compositions, and were also additionally exposed to hypoxia.[55,67,68] Collectively, it was demonstrated in male rats that proteinuria and/or albuminuria was significantly attenuated by transfer of RNO1, RNO5-8, RNO11, RNO13, RNO16, RNO18 and RNOY from BN into SS (Table 2).[55,67,68] Interestingly, in corresponding females introgression of each BN chromosome resulted in a significant reduction of proteinuria and/or albuminuria with the exception of RNO3, RNO15, RNO17 and RNOX (Table 2).[55,68] A sexual dimorphism with higher proteinuria levels in male compared with female SS rats was reported in another study and related to a functional effect of RNOX on proteinuria although this has not been confirmed and documented, for example, by data obtained in consomic strains.[67] Structural glomerular injury was significantly influenced by RNO1 in male rats (Table 2).[68]

In addition, transfer of BN-RNO13 (containing the renin gene) into consomic SS.BN13 ameliorated proteinuria levels, medullary interstitial fibrosis, glomerulosclerosis and tubular necrosis in response to high salt (4% NaCl; Table 2).[69]

Subsequently, in microarray analysis of kidneys from SS and SS.BN13 sequential changes in gene expression were uncovered for many differentially expressed genes on RNO13 (Table 3).[70] The microRNA miR-29b was found to affect different collagens and genes related to the extracellular matrix and thus might have a pivotal role in renal medullary injury of SS rats (Table 3).[71] Importantly, consomic and congenic strains derived from RNO13 shared not inevitably the same pathways identified in salt-sensitive hypertension and renal damage of the parental SS strain.[72] In further subcongenic breeding experiments, the QTL linked to proteinuria development on RNO13 was narrowed to a 1.9-Mb region, which however also affected BP (Table 3).[73]

FAWN-HOODED RAT

Strain breeding

The fawn-hooded rat model was selected from a cross of German-brown and white Lashley rats[16] and transferred early in 1970 by Tobach of the American Museum of Natural History as a closed outbred colony to Europe[74] and afterwards to Unilever Research Laboratories, Vlaardinger, The Netherlands.[16] Until the mid 1980s, hypertensive fawn-hooded rats were inbred and selected for high BP denoted as fawn-hooded hypertensive (FHH) or normotension (FHL, fawn-hooded low blood pressure).[75,76]

The August × Copenhagen (ACI, AxC9935) rat model is the established original reference strain for FHH and show resistance to hypertension, proteinuria and renal damage.[77,78]

Strain characteristics

The FHH strain is homozygous recessive for three coat color genes: *red-eyed dilution* (*r*), *nonagouti* (*a*) and *hooded* (*h*).[79,80] FHH develops hematuria[81] and a platelet storage-pool disease leading to a mild bleeding disorder,[74,82] which is based on a single-gene defect on RNO1 containing the *r* gene.[80] In addition, aging animals develop spontaneously systemic and glomerular hypertension and overt malignant nephrosclerosis with renal lesions such as FSGS,[83–87] podocyte injury[84,86] and progressive proteinuria and albuminuria.[77,81,88] Moreover, a sexual dimorphism with more aggravated hypertension and proteinuria in males compared with females is observed.[89] Overall, FHH have a shortened life expectancy.[84]

In contrast, FHL rats develop also chronic renal failure but less severe hypertension, only mild proteinuria and FSGS.[75]

Cosegregation and linkage analyses

Two linkage analyses in an (FHH/EUR × ACI)F1 × FHH backcross under normal conditions and in an (FHH/EUR × ACI/NCrEur)

Table 3 QTL fine mapping and candidate genes associated with renal disease of rat strains

Strain/reference phenotype	*QTL fine map on RNO*	*Size*	*Candidate genes*	*Gene alteration and/or pathophysiological function*
BUF[19,25,206]				
Proteinuria and FSGS	13: D13Got8-RN97596	—	Arp3	$^{L}111^{F}$ substitution in Arp3; actin assembly abnormalities in podocytes and influence on immunological processes of macrophages and Th2 lymphocytes.
FHH[1,97,98,103–105]				
Autoregulation of renal blood flow and renal disease	1: D1Rat20G17B-6-D1Rat888, Rf-1	4.3 Mb	Ins1 Olr385 Xpnpep1 Mxi1 Add3 Smndc1 DUSP-5 Smc3 Rbm20 Pdcd4 Shoc2	Glomerular hyperfiltration and rise in glomerular capillary pressure.
Proteinuria and FSGS	1: 143.4–144.9 Mb, Rf-2	1.5 Mb	Rab38	Protein null mutation (G→A) in the translation initiation start codon of Rab38. May modulate tubular processing of filtered albumin and proteins without affecting the glomerular filtration barrier leading to proteinuria. Also detected in a related FHH rat strain and several strains derived from the Long Evans rat.
Albuminuria and glomerulosclerosis	3: D3Got102-D3Got121, Rf-3	7.1 Mb	13 genes, i.e., Bcl2l1 Rem1	Bcl2l1 may be involved in renal tubular damage.
Glomerular permeability and glomerulosclerosis	14: D14Rat98-D14Hmgc18	4.1 Mb	—	One non-synonymous, intergenic, intronic, or untranslated variant(s) between ACI and FHH in this region leading to an increase in glomerular permeability and glomerulosclerosis.
MWF[143,144]				
Podocyte alterations	8: No fine mapping reported	—	—	Locus on RNO8 modulates podoplanin loss in podocytes.
SBH[150]				
Proteinuria	20: No fine mapping reported	—	Tubb5 (m, f) C2 (m, f) Ubd (m, f) Psmb8 (m, f)	Potential candidates identified by combined expression and positional candidate analysis.
SHR[170]				
Hypertension-induced renal damage	1: D1Mit1-Igf2 (D1Mgh22), overlap with Rf-2, Bpfh-1, possibly Rf-1	22 cM	—	—
SS[65,67,70–73,207]				
Proteinuria/albuminuria Glomerular, tubular and interstitial phenotypes	2: D2Arb11-Tpm3	1.5 cM, ~5 Mb	64 genes, i.e., Sfrp2 Wnt2b Cct3	Identification of the Wnt/β-catenin signalling pathway, in which *Sfrp2* and *Wnt2b* possibly lead to a modified fibrotic response primarily to renal damage in renal fibrosis. *Cct3* may affect cytoskeleton integrity.
Proteinuria, medullary interstitial fibrosis, glomerulosclerosis and tubular necrosis	13: No fine mapping reported	—	Gene list (see Liang *et al.*[70]) miR-29b	Several candidate pathways described by Liang *et al.*[70] with potential influence on collagens and extracellular matrix.
Proteinuria	13: D13Hmgc37-D13Got22	1.9 Mb	Nap5 (8 SNPs) LOC680596 LOC680652 Mgat5 Tmem163 LOC501853	Between SS and BN rats, eight SNPs could be identified in Nap5, of which five SNPs are synonymous.

Table 3 (Continued)

Strain/reference phenotype	QTL fine map on RNO	Size	Candidate genes	Gene alteration and/or pathophysiological function
Nephrotic-range proteinuria	18: No fine mapping reported	—	GATA-6	Apoptosis
SHRSP[170,185]				
Albuminuria and glomerulosclerosis	1: D1Mgh5-D1Arb21, including Rf-2	109 Mb	—	—

Abbreviations: *Add3*, adducin 3 (gamma); *Arp3*, actin-related protein 3; *Bcl2l1*, Bcl2-like 1; BUF, Buffalo; C2, Complement component 2; *Cct3,* chaperonin containing TCP1, subunit 3; *DUSP5*, dual specificity phosphatase 5; f, females; FHH, Fawn-hooded hypertensive; *Ins1*, insulin 1; *LOC501853,* similar to RAB3 GTPase-activating protein; *LOC680596,* hypothetical protein LOC680596; *LOC680652,* hypothetical protein LOC680652; m, males; miR, microRNA; *Mgat5,* mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase; *Mxi1*, MAX interactor 1; MWF, Munich Wistar Frömter; *Nap5*, Nck-associated protein 5; *Olr385*, olfactory receptor 385; *Pdcd4*, programmed cell death 4; *Psmb8*, Proteasome (prosome, macropain) subunit, beta type 8 (Large multifunctional peptidase 7); QTL, quantitative trait loci; *Rab38*, RAB38, member RAS oncogene family; *Rbm20*, RNA binding motif protein 20; *Rem1*, RAS (RAD and GEM)-like GTP-binding 1; SBH, Sabra hypertension prone; *Sfrp2,* secreted frizzled-related protein 2; *Shoc2*, soc-2 (suppressor of clear) homolog (*C. elegans*); SHR, spontaneous hypertensive rat; SHRSP, spontaneously hypertensive rat, stroke prone; SNP, single-nucleotide polymorphism; *Smc3*, structural maintenance of chromosomes 3; *Smndc1*, survival motor neuron domain containing 1; SS, Dahl salt-sensitive; *Tmem163*, transmembrane protein 163; *Tubb5*, Tubulin, beta 5 class I; *Ubd*, Ubiquitin D; *Wnt2b,* wingless-type MMTV integration site family, member 2B; *Xpnpep1*, X-prolyl aminopeptidase (aminopeptidase P) 1, soluble.

F2 cross subjected to unilateral nephrectomy (Nx) were performed in the FHH rat (Table 1).[77,90] The authors identified in both linkage studies overall five QTLs termed as *Rf* (renal failure) *1–5* locus, respectively; they are linked to renal damage, that is, proteinuria, albuminuria and/or focal glomerulosclerosis. *Rf-1* and *Rf-2* that are distinct from each other were mapped on RNO1, *Rf-3* on RNO3, *Rf-4* on RNO14 and *Rf-5* on RNO17 (Tables 1 and 5).[77,90] All *Rf* loci showed no significant effect on systemic BP, except RNO2.[77] An independent QTL on RNO1 (*Bpfh-1,* blood pressure in fawn-hooded-1) on RNO1[77] was also significantly linked to albuminuria and proteinuria (Tables 1 and 5).[90] Interestingly, in response to N^{ω}-nitro-L-arginine methyl ester (L-NAME) the *Rf-1* locus was also linked to functional and structural renal damage in FHL rats ascertained by genotype comparison between FHH and FHL.[78]

Lopez and associates demonstrated in a third linkage analysis in a female F2 population derived from consomic FHH-1BN/Mcwi and FHH/EurMcwi[66] a QTL on RNO1 showing a dominant mode of inheritance for impairment of renal blood flow autoregulation in FHH (Tables 1 and 5).[90,91] This QTL mapped to a 12.8-Mb region inside the *Rf-1* region (Table 3).[90,91]

Consomic/congenic studies

For QTL confirmation and QTL fine mapping, different consomic and congenic studies were generated between FHH and ACI or FHH and BN or for the genetic characterization of kidney injury in FHH.

FHH and ACI. Several congenic strains were established for QTL fine mapping analysis by transfer of different segments of FHH/EUR-*Rf* loci into the resistant ACI background (Table 2). Thus, in this experimental setting the occurrence of genetic susceptibility to kidney damage in ACI by transfer of *Rf* loci from FHH was tested. To enhance renal damage susceptibility, that is, albuminuria/proteinuria and focal glomerulosclerosis, in the resistant ACI background, however, animals were subjected to either unilateral nephrectomy (Nx) or NO inhibition by treatment with L-NAME or a combination of both procedures.[92–96] By using this protocol, different segments of the FHH-*Rf-1* region in five subcongenic ACI strains directly aggravated indeed the susceptibility of kidney damage and the autoregulation in congenic rats (Table 2).[92–96] Thus, the *Rf-1* locus contains at least one gene that might influence the susceptibility to progressive renal failure in the presence of higher BP values due to NO inhibition or Nx.[92]

Van Dijk *et al.*[93,95,96] demonstrated in a congenic *Rf-3* strain a slightly increased susceptibility to renal damage (Table 2), while single *Rf-4* and *Rf-5* congenics appeared normal in comparison with ACI, respectively.

In double-congenic studies, it was demonstrated that the susceptibility to renal damage in FHH was influenced by different synergistic gene–gene interactions.[90] Interestingly, it could be shown that in the FHH rat the *Rf-1* locus has marked additive effects on other *Rf* loci, that is, on *Rf-3* and *Rf-4* (Table 2),[90,93,95] while the interaction of *Rf-1* with *Rf-5* exhibited no significant effect on renal damage.[96]

To further narrow the *Rf-3* locus, two triple-congenic strains (Rf-1 + 3 + 4_a and Rf-1 + 3 + 4_b) were generated, which include different chromosomal segments of the *Rf-1*, *Rf-3* and *Rf-4* loci (Table 2). Subsequently, comparative genomics of the triple-congenic strains refined the Rf-3 region denoted as Rf-3_b to 7.1 Mb and 13 known or predicted genes, which directly influence renal impairment, that is, albuminuria, glomerulosclerosis and mean arterial pressure (Table 3). In the Rf-3_b region, pyrosequencing revealed several genes with non-synonomous amino-acid changes (Table 3).[97]

For fine mapping of the *Rf-4* locus, which spanned originally 61.9 Mb, only a 4.1-Mb segment of this FHH locus was introgressed in a minimal congenic Rf-1a + 4_a line of the ACI background (Table 2).[98] The authors stated that one non-synonymous, intergenic, intronic or untranslated variant(s) between ACI and FHH in the Rf-4_a segment may cause a loss of Nrf2 (Kelch-like ECH-associated protein 1) transcription factor binding site, which may lead to an increase in glomerular permeability to albumin and glomerulosclerosis without a BP influence in FHH rats (Table 3).[98] These findings seem to be of further interest, because the 4.1-Mb interval shows homology to human loci and QTL,[99,100] which were linked to renal function.[98]

FHH and BN. Mattson *et al.* followed the reciprocal approach and generated a full panel of consomic strains in which each autosome or sex chromosome of FHH/EurMcwi[66] was replaced by the corresponding BN/SSNHsdMcw chromosome. Male and female animals were subjected to NO inhibition by treatment with L-NAME and high-salt intake (8% NaCl) to aggravate renal damage

susceptibility, that is, albuminuria/proteinuria and structural kidney damage, in the FHH background. The authors demonstrated that renal disease phenotypes including proteinuria, albuminuria or glomerular injury are influenced by RNO1, RNO14, RNO15, RNO16 or RNO18 (Table 2).[101,102]

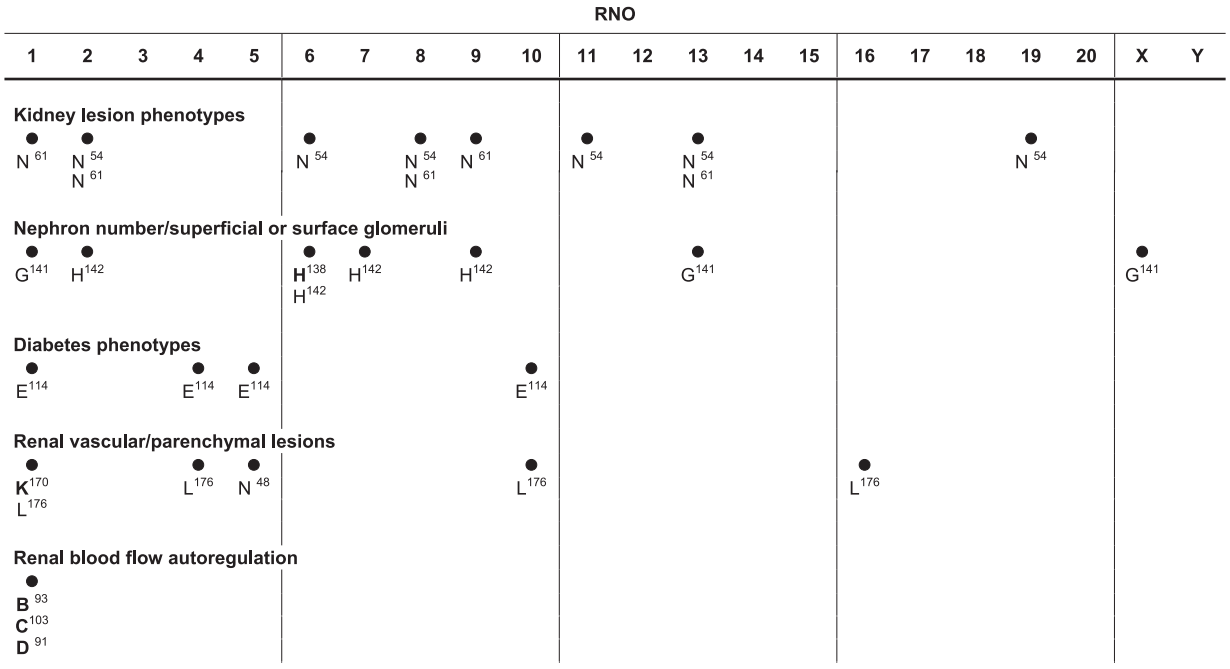
Further studies using BN as the reference strain for FHH generated new insights into the role of *Rf-1*. Thus, in the congenic FHH.1^{BN}AR^{+} strain autoregulation of renal blood flow was normalized and a decrease in the progression of renal disease was observed (Table 2).[91,103] It was suggested that before hypertension occurred an impaired autoregulation in FHH may lead to early onset of renal disease such as glomerulosclerosis and renal interstitial fibrosis.[103]

The genetic basis of albuminuria linked to the *Rf-2* on RNO1 was elucidated by identifying *Rab38* (RAB38, member RAS oncogene family) as a potential candidate gene within this locus.[104] An

Table 4.1 Distribution of QTL associated with renal (disease) phenotypes in the rat genome. A letter code for each cross or strain combination (specified in Legend Table 4.2) and corresponding references were listed below each QTL entry

	RNO																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	X	Y
Proteinuria	B 77 B 90 **B** 92 **B** 94 **C** 101 **C** 102 **C** 104 **D** 91 G 141 H 142 **I** 150 **I** 151 N 54 N 61 **O** 68	I 150 **I** 152 N 54 **N** 65 O 62 **O** 68	B 90 **B** 95 **I** 152 N 48	**O** 68	E 114 **O** 68	H 142 **I** 150 N 48 N 54 N 61 **O** 68	E 114 **O** 68	H 142 **N** 52 N 54 N 61 **O** 68	I 150 N 54 N 61 **N** 63 **N** 64 **O** 68	N 54 **O** 68	N 54 O 62 **O** 68 I 150	**O** 68	A 19 **F** 127 **I** 150 **N** 52 **O** 68 **O** 69 **O** 73	B 90 **C** 102 **O** 68	**C** 102 H 142	**C** 102 **O** 55 **O** 68	B 90 G 141 **I** 150 **I** 151 **I** 152	**O** 55 **O** 67 **O** 68	N 48 **N** 49 N 54 **O** 68	**I** 150 **I** 152 **O** 68		**O** 68
Albuminuria	B 90 **B** 92 **B** 94 **B** 96 **C** 101 **C** 102 **C** 104 G 141 H 142 **M** 185 N 54 N 61 **O** 68	N 53 N 54 **O** 68	B 90	H 142 **O** 68	**O** 68	G 141 **H** 138 H 142 **H** 143 J 168 N 48 N 53 N 54 N 61 **O** 68	H 142 **O** 68	**H** 139 H 142 **H** 143 **H** 144 N 48 **N** 52 N 53 N 54 N 61 **O** 68	H 142 N 48 N 53 N 54 N 61 **O** 68	N 53 N 54 **O** 68	N 53 N 54 **O** 68	G 141 **O** 68	**N** 52 N 54 N 61 **O** 68	B 90 **O** 68	**C** 102 H 142	**C** 102 **O** 55 **O** 68	B 90 G 141	**C** 102 **O** 55 **O** 68	N 48 **N** 49 N 53 N 54 **O** 68	**O** 68	H 142	**O** 68
Fibrosis		**N** 65				**H** 138 H 142		**H** 140 **N** 52					**N** 52 **O** 68							N 48		
Tubular damage		**N** 65	N 48		E 114	**H** 138	E 114	**H** 144 **N** 52					**N** 52 **O** 68 **O** 69									
Glomerular injury	B 77 B 90 **B** 92 **B** 93 **B** 94 **B** 96 **C** 101 **D** 91 **K** 170 **M** 185 **O** 68	**N** 65 O 62	B 90 **B** 95		E 114	**H** 138 **H** 143	E 114	**H** 143 **H** 144 **N** 52			O 62		**O** 68 O 69	**B** 98	**C** 102	**C** 102		**C** 102				

Table 4.1 (Continued)



●, QTL identified in linkage analysis (letter code for cross in normal font) or QTL confirmed by consomic/congenic studies (letter code for strains in bold); QTL, quantitative trait loci; RNO, rat chromosome.

Table 4.2 Legend for Table 4.1

Label	*Cross/strains*	*References*
A	BUF × WKY	19
B	FHH × ACI	77, 90, 92, 93, 94, 95, 96, 98
C	FHH × BN	101, 102, 103, 104
D	FHH.1BN × FHH	91
E	GK × BN	114
F	LH × BN	127
G	MWF × Lew	141
H	MWF × SHR	138, 139, 140, 142, 143, 144
I	SBH × SBN	150, 151, 152
J	SHR-A3 × SHR-B2	168
K	SHR × BN	170
L	SHRSP × SHR	176
M	SHRSP × WKY	185
N	SS × SHR	48, 49, 52, 53, 54, 61, 63, 64, 65
O	SS × BN	55, 62, 67, 68, 69, 73

Abbreviations: ACI, August × Copenhagen Irish; BN, Brown Norway; BUF, Buffalo; FHH, Fawn-hooded hypertensive; GK, Goto-Kakizaki; Lew, Lewis; LH, Lyon hypertensive; Lew, Lewis; MWF, Munich Wistar Frömter; SBH, Sabra hypertension prone; SBN, Sabra hypertension resistant; SHR, spontaneously hypertensive rat; SHRSP, spontaneously hypertensive rat, stroke prone; SS, Dahl salt-sensitive; WKY, Wistar-Kyoto.

interesting study by Rangel-Filho *et al.* reported a protein null mutation (G→A) in the translation initiation start codon of *Rab38* in FHH (Table 3).[104,105] The exchange of *Rf-2* including *Rab38* and seven other genes led to the restoration of *Rab38* protein expression and a significant reduction of increased albuminuria and proteinuria in congenic FHH.BN-Rab38 compared with FHH (Table 3).[104] In FHH, *Rab38* may modulate the tubular processing of filtered proteins without affecting the glomerular filtration barrier leading to proteinuria.[104]

GOTO-KAKIZAKI RAT

Strain breeding

In 1973, the Goto-Kakizaki (GK) rat model was selected by inbreeding from a non-diabetic Wistar rat colony in Sendai, Japan.[106–109] GK rats demonstrate glucose intolerance upon oral glucose tolerance tests, and a colony was transferred to Europe in 1989.[110]

Strain characteristics

The GK rats are not obese and develop in both sexes spontaneously with early onset glucose intolerance and mild hyperglycemia, and thus non-insulin-dependent diabetes mellitus.[108,110–114] In addition, other phenotype such as salt-sensitive hypertension,[115] hypertriglyceridemia, endothelial dysfunction,[115] microangiopathy and macroangiopathy were observed in GK.[110] Older animals develop significant renal damage including glomerular hypertrophy, thickening of the glomerular basement membrane, proliferation of mesangial cells, glomerulosclerosis, tubulointerstitial fibrosis and inflammatory cell infiltration.[113,116–118] Moreover, some substrains of GK develop increased proteinuria at 24 months of age,[118] which might be affected by hypertension.[119] Furthermore, GK rats show early development of neuropathy and retinopathy late in life.[110]

Cosegregation and linkage analyses

Nobrega *et al.*[114] identified in a genome-wide analysis of a salt fed (1% NaCl) GK_{FL} × BN/Mcwi F2 population four loci on RNO1, RNO4, RNO5 and RNO10 linked to early diabetes phenotypes (Tables 1 and 5). Furthermore, from two proteinuria QTLs identified on RNO5 and RNO7, only the QTL on RNO5 colocalized with a diabetes QTL (Tables 1 and 5). Both proteinuria QTLs were also linked to glomerulosclerosis and tubular sclerosis.[114] These data indicate that diabetes and proteinuria development in the GK rat model were affected by different genetic mechanisms.[114] Further

Table 5 Chromosomal mapping and colocalizations of renal disease QTL identified in genome-wide linkage analyses of genetic rat models

QTL on RNO	QTL interval[a] or peakmarker[b]	Start position	Stop position	Phenotype	Cross	Sex	Ref.
1	D1Rat238	3 897 423	—	Renal vascular/parenchymal lesions	SHRSP × SHR F2	m, f	176
1 (Rf-2)	D1Mit20–D1Mit4[c]	94 356 876 (or 94 582 077)	160 000 000[d]	Focal glomerulosclerosis	FHH × ACI BC	m	77
1 (Rf-2)	D1Mit20–D1Mgh26	94 356 876 (or 94 582 077)	176 616 212	Focal glomerulosclerosis	FHH × ACI F2	m	90
1	Kallikrein locus	94 692 856	—	Renal vascular/parenchymal lesions	SHRSP × SHR F2	m, f	176
1 (QTL1)	D1Rat31–D1Rat216	107 734 739	185 923 619	Albuminuria	MWF × Lew BC	m	141
1 (Bpfh1)	D1Wox6–D1Mgh26	131 956 600	176 616 212	Albuminuria	FHH × ACI F2	m	90
1 (Rf-2)	D1Wox6–D1Mgh26	131 956 600	176 616 212	Albuminuria	FHH × ACI F2	m	90
1 (Rf-2)	D1Wox6–D1Mgh26	131 956 600	176 616 212	Proteinuria	FHH × ACI F2	m	90
1 (Bpfh1)	D1Wox6–D1Mgh26	131 956 600	176 616 212	Proteinuria	FHH × ACI F2	m	90
1 (QTL 1)	D1Rat38–D1Rat236	133 566 681	155 183 662	Proteinuria	MWF × Lew BC	m	141
1	D1Rat43[c]	138 300 000[d]	—	Creatinine levels	LH × LN F2	m	126
1 (Rf-2)	***Rab38***	144 783 919	144 864 573	Proteinuria	FHH × ACI	m	104,105
1	D1Rat278	168 930 690	168 930 831	Kidney weight	LH × LN F2	m	126
1	D1Mco29–D1Rat86	186 471 762	259 173 488	Albuminuria	SS × SHR BC	m	54
1	D1Mco29–D1Rat86	186 471 762	259 173 488	Albuminuria	SS × SHR F2	m	61
1	D1Mco29–D1Rat86	186 471 762	259 173 488	Kidney lesion grade	SS × SHR F2	m	61
1	D1Mco29–D1Rat86	186 471 762	259 173 488	Proteinuria	SS × SHR F2	m	61
1	D1Rat287–D1Rat89	190 114 248	265 343 617	Renal blood flow autoregulation	FHH.1^{BN} × FHH F2	f	91
1	D1Rat188	206 567 644	—	Kidney weight	LH × LN F2	m	126
1 (Rf-1)	D1Mgh11[c] (D1Rat383[e])–D1Mit8	209 205 489	257 363 728	Albuminuria	FHH × ACI F2	m	90
1 (Rf-1)	D1Mgh11[c] (D1Rat383[e])–D1Mit8	209 205 489	257 363 728	Focal glomerulosclerosis	FHH × ACI F2	m	90
1 (QTL2)	D1Rat71–D1Rat90	216 663 010	267 111 087	Albuminuria	MWF × SHR BC	m	142
1 (QTL 2)	D1Rat71–D1Rat90	216 663 010	267 111 087	Proteinuria	MWF × SHR BC	m	142
1	D1Uia5–D1Rat86	219 804 772	259 173 488	Proteinuria	SS × SHR BC	m	54
1	D1Mit18	224 426 267	—	Kidney weight	LH × LN F2	m	126
1 (Rf-1)	D1Mit6[c] (D1Mit18[e])–D1Mit8	224 426 267	257 363 728	Focal glomerulosclerosis	FHH × ACI BC	m	77
1 (Rf-1)	D1Mit6[c] (D1Mit18[e])–D1Mit8	224 426 267	257 363 728	Proteinuria	FHH × ACI BC	m	77
1	D1Rat75–D1Mgh13	235 098 674	252 340 527	Diabetes phenotypes	GK × BN F2	m	114
1 (Rf-1)	D1Rat119–D1Mit8	242 586 139	257 363 728	Proteinuria	FHH × ACI F2	m	90
1	D1Rat151[c]	250 670 000[d]	—	Surface glomeruli	MWF × Lew BC	m	141
1 (Rf-1)	***Ins1***	258 001 134	258 001 688	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Olr385***	258 055 709	258 064 088	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Xpnpep1***	259 089 652	259 139 681	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Mxi1***	259 219 584	259 259 979	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Add3***	259 347 673	259 455 407	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Smndc1***	259 596 813	259 607 340	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***DUSP5***	259 754 234	259 767 645	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Smc3***	259 822 480	259 865 602	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Rbm20***	259 905 545	260 144 190	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Pdcd4***	260 183 648	260 202 032	May cause renal function	FHH × BN	m	103
1 (Rf-1)	***Shoc2***	260 255 253	260 273 170	May cause renal function	FHH × BN	m	103
2	D2Rat194–D2Rat276	29 237 361	83 276 916	Proteinuria	SS × BN F2	f	62
2	D2Rat14[c]	41 000 000[d]	—	Superficial glomeruli	MWF × SHR BC	m	142
2	D2Rat32[c] (D2Mit5[e])–D2Rat54	66 680 022	210 012 267	Proteinuria	SBH × SBN F2	m	152
2	D2Mco18–D2Rat61	79 796 834	227 150 249	Kidney lesion grade	SS × SHR F2	m	61
2	D2Mco18–D2Rat61	79 796 834	227 150 249	Proteinuria	SS × SHR BC	m	54
2	D2Rat30–D2Rat70	116 504 241	254 933 362	Proteinuria	SBH × SBN BC	m	150
2	D2Rat217–D2Rat82	121 545 311	214 633 868	Albuminuria	SS × SHR BC	m	54
2	D2Rat217–D2Rat61	121 545 311	227 150 249	Kidney lesion grade	SS × SHR BC	m	54
2	D2Rat93	133 459 410	—	Kidney weight	LH × LN F2	m	126
2	D2Rat147–D2Mgh12	138 700 980	210 636 169	Focal glomerulosclerosis	SS × BN F2	f	62
2	D2Rat221	145 754 797	—	Creatinine levels	LH × LN F2	m	126
2	D2Rat36[c]–D2Rat57	163 100 000[d]	218 568 266	Albuminuria	SS × SHR F2	m	53
2	***Sfrp2***	175 479 320	175 486 865	May lead to a modified fibrotic response	SS × SHR	m	65
2	***Cct3***	180 381 044	180 434 152	primarily to renal damage in renal	SS × SHR	m	65
2	***Wnt2b***	200 218 630	200 233 002	fibrosis	SS × SHR	m	65

Table 5 (Continued)

QTL on RNO	QTL interval[a] or peakmarker[b]	Start position	Stop position	Phenotype	Cross	Sex	Ref.
3	D3Mgh9–D3Rat117	4 010 231	25 297 184	Proteinuria	SS × SHR F2	m	48
3	D3Mgh9	4 010 231	—	Tubulointerstitial inflammation grading	SS × SHR F2	m	48
3	D3Arb8	60 697 027	—	Kidney weight	LH × LN F2	m	126
3	D3Rat31–D3Mgh1	76 620 759	163 778 754	Proteinuria	SBH × SBN F2	m	152
3 (Rf-3)	D3Mit4	131 188 559	—	Albuminuria	FHH × ACI F2	m	90
3 (Rf-3)	D3Mit4	131 188 559	—	Focal glomerulosclerosis	FHH × ACI F2	m	90
3 (Rf-3)	D3Mit4	131 188 559	—	Proteinuria	FHH × ACI F2	m	90
3 (Rf-3)	***Rem1***	142 976 928	142 985 368	May cause renal function	FHH × ACI	m	97
3 (Rf-3)	***Bcl2l1***	143 129 087	143 180 199	May cause renal function	FHH × ACI	m	97
4	D4Rat1–D4Rat22	6 690 730	60 974 511	Diabetes phenotypes	GK × BN F2	m	114
4	D4Rat95	131 141 780	—	Albuminuria	MWF × SHR BC	m	142
4	D4Mgh7[c]	150 000 000[d]	—	Renal vascular/parenchymal lesions	SHRSP × SHR F2	m, f	176
5	D5Mgh2–D5Rat26	17 517 135	119 333 217	Diabetes phenotypes	GK × BN F2	m	114
5	D5Mit10	57 974 568	—	Microangiopathy	SS × SHR F2	m	48
5	D5Rat13	76 605 418	—	Proteinuria	GK × BN F2	m	114
5	D5Rat13	76 605 418	—	Glomerulosclerosis	GK × BN F2	m	114
5	D5Rat13	76 605 418	—	Tubular sclerosis	GK × BN F2	m	114
6 (QTL1)	D6Rat80–D6Mit9	1 301 953	34 039 304	Albuminuria	SS × SHR F2	m	48
6 (QTL1)	D6Rat46–D6Rat84[c] (D6Uia3[e])	13 286 616	46 050 011	Proteinuria	SS × SHR BC	m	54
6 (QTL1)	D6Rat108–D6Mit9	16 302 146	34 039 461	Proteinuria	SS × SHR F2	m	48
6	D6Rat135–D6Rat165	49 087 616	93 819 252	Proteinuria	SBH × SBN BC	m	150
6 (QTL1)	D6Rat95–D6Rat12	54 887 959	114 032 160	Albuminuria	MWF × Lew BC	m	141
6 (QTL2)	D6Rat106–D6Rat6	68 036 230	123 455 207	Albuminuria	MWF × SHR BC	m	142
6 (QTL2)	D6Rat106–D6Rat6	68 036 230	123 455 207	Proteinuria	MWF × SHR BC	m	142
6 (QTL2)	D6Mit3–D6Wox13	75 049 528	136 452 267	Albuminuria	SS × SHR BC	m	54
6 (QTL2)	D6Mit3–D6Wox13	75 049 528	136 452 267	Albuminuria	SS × SHR F2	m	61
6 (QTL2)	D6Mit3–D6Wox13	75 049 528	136 452 267	Proteinuria	SS × SHR BC	m	54
6 (QTL2)	D6Mit3–D6Wox13	75 049 528	136 452 267	Proteinuria	SS × SHR F2	m	61
6 (QTL2)	D6Rat104–D6Rat6	88 723 451	123 455 207	Albuminuria	SS × SHR F2	m	53
6	D6Mit8	97 561 874	—	Renal interstitial fibrosis	MWF × SHR BC	m	142
6	D6Mit8	97 561 874	—	Superficial glomeruli	MWF × SHR BC	m	142
6	D6Uia5–D6Wox13	113 959 391	136 452 267	Kidney lesion grade	SS × SHR BC	m	54
6	D6Rat12	114 032 010	—	Surface glomeruli	MWF × SHR BC	m	142
6 (QTL2)	D6Rat6–D6Rat4	123 455 031	144 200 901	Albuminuria	SS × SHR F2	m	48
6	Igh (LOC366772) locus	138 250 040	138 452 782	Immunoglobulin G subclasses associated with albuminuria	SHR-A3 × SHR-B2 F2	m	168
7	D7Mgh6	96 648 985	—	Glomerulosclerosis	GK × BN F2	m	114
7	D7Mgh6	96 648 985	—	Proteinuria	GK × BN F2	m	114
7	D7Mgh6	96 648 985	—	Tubular sclerosis	GK × BN F2	m	114
7	D7Rat7	126 394 716	—	Superficial glomeruli	MWF × SHR BC	m	142
7	D7Rat4	134 614 034	—	Albuminuria	MWF × SHR BC	m	142
8	D8Rat53–D8Rat19	19 815 643	98 451 403	Albuminuria	MWF × SHR BC	m	142
8	D8Rat53–D8Rat20	19 815 643	94 870 319	Albuminuria	SS × SHR F2	m	53
8	D8Rat53–D8Rat12	19 815 643	108 654 668	Proteinuria	MWF × SHR BC	m	142
8	D8Mit5–D8Rat130	32 203 395	98 986 263	Albuminuria	SS × SHR BC	m	54
8	D8Mit5–D8Rat130	32 203 395	98 986 263	Albuminuria	SS × SHR F2	m	61
8	D8Mit5–D8Rat130	32 203 395	98 986 263	Kidney lesion grade	SS × SHR F2	m	61
8	D8Mit5–D8Rat133	32 203 395	94 514 282	Proteinuria	SS × SHR BC	m	54
8	D8Mit5–D8Rat130	32 203 395	98 986 263	Proteinuria	SS × SHR F2	m	61
8	D8Mit3–D8Rat133	45 291 675	94 514 282	Kidney lesion grade	SS × SHR BC	m	54
8	D8Rat39–D8Rat20	49 035 744	94 870 319	Albuminuria	SS × SHR F2	m	48
9 (QTL2)	D9Mgh5–D9Uia4	2 176 483	59 247 627	Albuminuria	SS × SHR BC	m	54
9	D9Rat29–D9Rat3	22 066 241	99 799 902	Albuminuria	MWF × SHR BC	m	142
9	D9Rat29–D9Rat71	22 066 241	106 234 825	Albuminuria	SS × SHR F2	m	53
9	D9Rat29–D9Rat5	22 066 241	85 187 003	Albuminuria	SS × SHR F2	m	48

Table 5 (Continued)

QTL on RNO	QTL interval[a] or peakmarker[b]	Start position	Stop position	Phenotype	Cross	Sex	Ref.
9 (QTL1)	D9Rat26–D9Mco6	37 313 134	105 580 061	Albuminuria	SS × SHR BC	m	54
9	D9Rat26–D9Rat97[c] (D9Mco6[e])	37 313 134	105 580 061	Proteinuria	SS × SHR BC	m	54
9	D9Uia4–D9Mco6	59 247 347	105 580 061	Albuminuria	SS × SHR F2	m	61
9	D9Uia4–D9Mco6	59 247 347	105 580 061	Kidney lesion grade	SS × SHR F2	m	61
9	D9Uia4–D9Mco6	59 247 347	105 580 061	Proteinuria	SS × SHR F2	m	61
9	D9Mit5–D9Rat109	75 633 468	100 495 220	Proteinuria	SBH × SBN BC	m	150
9	D9Rat5	85 186 878	—	Superficial glomeruli	MWF × SHR BC	m	142
10	D10Mit6–D10Rat2[c] (D10Rat134[e])	14 721 136	108 557 588	Diabetes phenotypes	GK × BN F2	m	114
10	D10Rat43–D10Rat93	23 428 128	81 887 390	Albuminuria	SS × SHR F2	m	53
10	D10Rat38–D10Mco66	31 668 581	82 143 815	Albuminuria	SS × SHR BC	m	54
10	D10Rat38–D10Mco66	31 668 581	82 143 815	Proteinuria	SS × SHR BC	m	54
10	D10Rat168	39 032 756	—	Kidney weight	LH × LN F2	m	126
10	D10Rat21–D10Rat55 (Rbp4g locus)	83 527 878	89 167 279	Renal vascular/parenchymal lesions	SHRSP × SHR F2	m, f	176
11	D11Rat31–D11Rat50	8 176 273	84 841 212	Albuminuria	SS × SHR BC	m	54
11	D11Rat31–D11Rat50	8 176 273	84 841 212	Proteinuria	SS × SHR BC	m	54
11	D11Rat20–D11Rat6	16 670 275	45 232 942	Albuminuria	SS × SHR F2	m	53
11	D11Rat15–D11Rat38	29 744 438	62 045 696	Glomerular injury	SS × BN F2	f	62
11	D11Rat71–D11Rat61[c] (D11Rat62[e])	41 711 172	69 538 204	Proteinuria	SS × BN F2	f	62
11	D11Rat67–D11Rat50	45 797 511	84 841 212	Kidney lesion grade	SS × SHR BC	m	54
11	D11Rat7–D11Mgh2[c] (D11Rat42[e])	46 499 942	79 034 468	Proteinuria	SBH × SBN BC	f	150
12	D12Rat59–D12Mgh5	4 864 405 (or 155 314)	29 130 304	Albuminuria	MWF × Lew BC	m	141
13	D13Rat1–D13Rat63	10 555 731	80 482 429	Albuminuria	SS × SHR BC	m	54
13	D13Rat1–D13Rat61	10 555 731	68 034 927	Albuminuria	SS × SHR F2	m	61
13	D13Rat1–D13Rat61	10 555 731	68 034 927	Kidney lesion grade	SS × SHR F2	m	61
13	D13Got8–Rn97596	37 191 204	43 542 044	Proteinuria	BUF × WKY BC	m	19
13	***Arp3***	37 861 558	37 904 589	May cause proteinuria	BUF × WKY	m	19
13	***Nap5***	38 444 115	39 275 959	May cause proteinuria	SS × BN	m	73
13	D13Mgh4–D13Mgh6	38 489 802	63 301 552	Proteinuria	SBH × SBN	f	150
13	***LOC680596***	39 619 022	39 620 110	May cause proteinuria	SS × BN	m	73
13	***LOC680652***	39 764 191	39 801 771	May cause proteinuria	SS × BN	m	73
13	***Mgat5***	39 900 089	40 135 002	May cause proteinuria	SS × BN	m	73
13	***Tmem163***	40 144 073	40 327 947	May cause proteinuria	SS × BN	m	73
13	***LOC501853***	40 419 938	40 432 494	May cause proteinuria	SS × BN	m	73
13	D13Rat62	60 679 880	—	Surface glomeruli	MWF × Lew BC	m	141
13	D13Mgh5–D13Mgh6	63 301 413	101 704 301	Kidney lesion grade	SS × SHR BC	m	54
13	**miR29b** (rno-mir-29b-2)	110 967 520	110 967 600	May cause renal medullary injury	SS × BN	m	71
14 (Rf-4)	D14Mgh7	11 567 182	—	Albuminuria	FHH × ACI F2	m	90
14 (Rf-4)	D14Mgh7	11 567 182	—	Proteinuria	FHH × ACI F2	m	90
14 (Rf-4)	**Intergenic variant(s)**	17 821 228	—	May cause a loss of Nrf2 transcription factor binding site	FHH × ACI	m	98
15	D15Rat66	21 851 206	—	Proteinuria	MWF × SHR BC	m	142
15	D15Rat102	97 700 575	—	Albuminuria	MWF × SHR BC	m	142
16	D16Mit2	4 304 397	—	Renal vascular/parenchymal lesions	SHRSP × SHR F2	m, f	176
17	D17Rat1–D17Rat67	5 583 327	35 394 345	Proteinuria	SBH × SBN F2	m	152
17	D17Rat2–D17Rat17	9 988 754	42 344 987	Kidney weight	LH × LN F2	m	126
17	D17Rat94[c] (D17Rat86[e])–D17Rat58	18 278 604	81 039 648	Creatinine levels	LH × LN F2	m	126
17 (Rf-5)	D17Mit12 (Spl6 locus)	26 570 057	71 570 057	Albuminuria	FHH × ACI F2	m	90
17 (Rf-5)	D17Mit12 (Spl6 locus)	26 570 057	71 570 057	Proteinuria	FHH × ACI F2	m	90
17	D17Rat33–D17Rat133	70 864 165	91 948 193	Albuminuria	MWF × Lew BC	m	141
17	D17Rat58	81 039 506	—	Proteinuria	MWF × Lew BC	m	141
19	D19Rat34–D19Uia1[c] (D19Wox1[e])	2 265 038	46 087 922	Albuminuria	SS × SHR BC	m	54
19	D19Rat86[c] (D19Rat34[e])–D19Rat57	2 265 038	57 234 989	Albuminuria	SS × SHR F2	m	48

Table 5 (Continued)

QTL on RNO	QTL interval[a] or peakmarker[b]	Start position	Stop position	Phenotype	Cross	Sex	Ref.
19	D19Rat34–D19Uia1[c] (D19Wox1[e])	2 265 038	46 087 922	Kidney lesion grade	SS × SHR BC	m	54
19	D19Rat34–D19Uia1[c] (D19Wox1[e])	2 265 038	46 087 922	Proteinuria	SS × SHR BC	m	54
19	D19Rat86[c] (D19Rat34[e])–D19Rat2	2 265 038	55 455 363	Proteinuria	SS × SHR F2	m	48
19	D19Rat19–D19Mit7	7 813 538	45 090 916	Albuminuria	SS × SHR F2	m	53
20	***Ubd***	1 475 944	1 477 895	May cause proteinuria	SBH × SBN	m, f	150
20	***Tubb5***	3 060 224	3 090 776	May cause proteinuria	SBH × SBN	m, f	150
20	***C2***	4 051 146	4 071 909	May cause proteinuria	SBH × SBN	m, f	150
20	D20Rat41–D20Rat5	4 740 610	18 411 969	Proteinuria	SBH × SBN BC	m, f	150
20	***Psmb8***	4 786 260	4 789 223	May cause proteinuria	SBH × SBN	m, f	150
20	D20Rat32–D20Rat27	4 977 627	28 656 743	Proteinuria	SBH × SBN F2	m	152
20	D20Rat12	32 880 867	—	Renal interstitial fibrosis	SS × SHR F2	m	48
X	DXRat8	41 386 879	—	Albuminuria	MWF × SHR BC	m	142
X	DXRat96	122 069 706	—	Superficial glomeruli	MWF × Lew BC	m	141

Abbreviations: ACI, August × Copenhagen Irish; Backcross, BC; BN, Brown Norway; BUF, Buffalo; f, females; FHH, Fawn-hooded hypertensive; GK, Goto-Kakizaki; Lew, Lewis; LH, Lyon hypertensive; LN, Lyon normotensive; Lew, Lewis; m, males; miR, microRNA; MWF, Munich Wistar Frömter; QTL, quantitative trait loci; Ref., reference; RNO, rat chromosome; SBH, Sabra hypertension prone; SBN, Sabra hypertension resistant; SHR, spontaneously hypertensive rat; SHRSP, spontaneously hypertensive rat, stroke prone; SS, Dahl salt-sensitive; WKY, Wistar-Kyoto. Candidate genes are given in bold: *Add3*, adducin 3 (gamma); *Arp3*, actin-related protein 3; *Bcl2l1*, Bcl2-like 1; C2, Complement component 2; *Cct3*, chaperonin containing TCP1, subunit 3; *DUSP5*, dual specificity phosphatase 5; *Ins1*, insulin 1; *LOC501853*, similar to RAB3 GTPase-activating protein; *LOC680596*, hypothetical protein LOC680596; *LOC680652*, hypothetical protein LOC680652; *Mgat5*, mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase; *Mxi1*, MAX interactor 1; *Nap5*, Nck-associated protein 5; *Olr385*, olfactory receptor 385; *Pdcd4*, programmed cell death 4; *Psmb8*, Proteasome (prosome, macropain) subunit, beta type 8 (Large multifunctional peptidase 7); *Rab38*, RAB38, member RAS oncogene family; *Rbm20*, RNA binding motif protein 20; *Rem1*, RAS (RAD and GEM)-like GTP-binding 1; *Shoc2*, soc-2 (suppressor of clear) homolog (C. elegans); *Sfrp2*, secreted frizzled-related protein 2; *Smc3*, structural maintenance of chromosomes 3; *Smndc1*, survival motor neuron domain containing 1; *Tmem163*, transmembrane protein 163; *Tubb5*, Tubulin, beta 5 class I; *Ubd*, Ubiquitin D; *Wnt2b*, wingless-type MMTV integration site family, member 2B; *Xpnpep1*, X-prolyl aminopeptidase (aminopeptidase P) 1, soluble.

[a]QTL mapping was carried out by the 2-logarithm of odds (LOD) interval for placement of each QTL as recommended by Lander and Kruglyak.[205] For original studies in which LOD intervals were not reported, corresponding 2-LOD intervals were estimated by the authors of this review. Importantly, both the marker intervals and subsequently the start and stop positions of each QTL interval represent only approximate values.

[b]In several studies, only the peak marker of the identified QTLs were reported and given in Table 5 as indicated by 'start position'.

[c]Positional localization by RGSC Genome Assembly v3.4 were not reported in Rat Genome Database (RGD, http://www.rgd.mcw.edu/). Light and dark grey colors represent main colocalizations between QTL.

[d]Position estimated by flanking markers.

[e]Position given by this next flanking marker.

analysis showed that diabetes in GK rats might be affected by chronic inflammatory processes.[120] More recently, renal and circulating *Nsa2* (Nop-7-associated 2) levels were elevated in GK rats and associated with the development of diabetic nephropathy in this strain.[121]

No consomic or congenic studies were reported.

LYON HYPERTENSIVE RAT

Strain breeding

The Lyon hypertensive (LH) rat strain was established in 1969 by breeding of outbred Sprague-Dawley rats, which were selected for high systolic BP.[122] In addition, the control strains Lyon normotensive (LN) and Lyon low blood pressure strain were generated.[16,122,123]

Strain characteristics

LH rats demonstrate mild spontaneous, salt-sensitive hypertension, proteinuria and albuminuria and exhibit several features common to the human metabolic syndrome including dyslipidemia, insulin resistance and glucose intolerance.[124–127]

Cosegregation and linkage analyses

Two linkage analyses were performed by using a male LH × LN F2 population for BP, anthropometry, renal, metabolic and endocrine phenotypes.[124,126] For the renal phenotype, data QTL were demonstrated for creatinine levels on RNO1, RNO2 and RNO17 and for kidney weight phenotypes on RNO1–RNO3, RNO10 and RNO17, while no linkage for proteinuria, albuminuria or structural kidney damages was reported (Table 1).[126] In addition, several QTLs linked to BP could be detected on RNO2, RNO13 and RNO17.[126]

Consomic studies

Gilibert *et al.*[127] confirmed in consomic studies using BN as a reference strain in an LH-13^{BN} consomic strain, in which BN/NHsdMcwi-RNO13 was transferred into the LH background, the functional relevance of the RNO13 carrying BP-QTL (Table 2).

Interestingly, the LH-13^{BN} consomic strain exhibits a 50% reduction in proteinuria in LH-13^{BN} compared with LH.[127] However, it could be not clarified whether the amelioration in proteinuria depends on the lower BP observed in the congenic strain or whether genetic factors on RNO13 control the proteinuria development.[127] In contrast, reciprocal introgression of LH-RNO13 into the BN background is not capable of inducing a proteinuria phenotype in the consomic strain BN-13^{LH}.[127]

MUNICH WISTAR FRÖMTER RAT

Strain breeding

The Munich Wistar Frömter (MWF) rat strain was originally selected over several generations for the presence of an increased number of surface glomeruli and originally established as a colony (MWF/Ztm) in Hannover, Germany.[128,129] The colony MWF/$_{FUB}$ renamed as MWF/$_{Rkb}$ and more recently to MWF/FubRkb was established in 1996 by further inbreeding of rats from the original colony at the Charité – Universitätsmedizin Berlin, Germany.[130]

Strain characteristics

MWF rats develop mild SS spontaneous hypertension, spontaneous albuminuria of early onset, structural renal abnormalities such as an inherited nephron reduction of 30–50%, glomerulosclerosis, reduced podocyte number, renal interstitial fibrosis and endothelial dysfunction.[130–139] Moreover, a sexual dimorphism leads to a more severe

manifestation and progression of albuminuria and subsequent renal failure in males compared with females.[130,133,140]

Cosegregation and linkage analyses

Schulz *et al.* performed two genome-wide linkage analyses in backcross populations between MWF and a normotensive (Lewis/$_{FUB}$) and a hypertensive (SHR/$_{FUB}$) reference strain and identified overall 11 different QTLs on 10 rat chromosomes including RNO1 (QTL1 and QTL2), RNO4, RNO6–RNO9, RNO12, RNO15, RNO17 and RNOX, which accounted for albuminuria development in MWF (Tables 1 and 5).[130,141,142] In addition, six QTLs on RNO1 (QTL1 and QTL2), RNO6, RNO8, RNO15 and RNO17 were linked to proteinuria, and one QTL was linked to renal interstitial fibrosis on RNO6 (Tables 1 and 5).[141,142] Only the albuminuria QTL on RNO6 was identified in both crosses. Overall, the QTL on RNO6 and the QTL on RNO8, which was only detected in the cross between MWF and SHR, exhibited the strongest linkage and phenotypic effects on albuminuria.[141,142] Furthermore, seven QTLs on RNO1–RNO2, RNO6–RNO7, RNO9, RNO13 and RNOX were linked to the number of superficial or surface glomeruli (Tables 1 and 5), while the total number of nephrons was not analyzed in these QTL-mapping studies.[141,142]

Consomic studies

The functional role of both major albuminuria QTLs on RNO6 and RNO8 was confirmed by transfer of either RNO6 or RNO8 from SHR into the MWF background.[138–140] Thus, in both single-consomic strains MWF-6^{SHR} and MWF-8^{SHR}, the progressive albuminuria observed in aging male and female MWF was significantly ameliorated (Table 2).[138–140] Interestingly, the nephron deficit observed in MWF (-36% *vs* SHR) was linked to RNO6, since total nephron number was only normalized by replacement of RNO6 but not of RNO8 in consomic strains (Table 2).[138,139] Recently, double-consomic studies in MWF-6^{SHR}8^{SHR} by double transfer of SHR-RNO6 and SHR-RNO8 into MWF confirmed a strong synergistic effect between QTL on RNO6 and RNO8, since the albuminuria and associated structural kidney damage phenotypes were completely abolished in the double-consomic strain (Table 2).[143]

In a reciprocal single-consomic strain, transfer of MWF-RNO8 into the isolated albuminuria-resistant SHR background caused an induction of albuminuria already under normal conditions, while an increase in structural glomerular damage was only detected after Nx in consomic SHR-8^{MWF} (Table 2).[144] Thus, the results demonstrate the independent role of MWF QTL on RNO8 for both albuminuria and structural kidney damage.[144] In contrast, MWF-RNO6 failed to induce an albuminuria phenotype either under control conditions or in response to a 50% nephron reduction after Nx in consomic SHR-6^{MWF}.[145]

SABRA RAT

Strain breeding

The original Sabra colonies of hypertension-prone (H) and hypertension-resistant (N) strains were developed by Ben-Ishay at the Hebrew University Medical Center in Jerusalem, Israel. Rats were selected for high BP values due to Nx, treatment with deoxycorticosterone acetate, and 1% NaCl.[146,147] This original and not fully inbred colony was terminated in 1992, when a subset of rats was transferred to the Ben-Gurion University Barzilai Medical Center in Ashkelon, Israel. Subsequently, two new genetically and phenotypically homogeneous colonies of Sabra hypertension-prone (SBH/y) and hypertension-resistant (SBN/y) rats were further developed.[148]

Strain characteristics

The inbred Sabra strains represent a model of salt sensitivity; the substrain SBH/y shows salt sensitivity, while the substrain SBN/y is salt resistant.[148,149] Both inbred Sabra strains are normotensive during life when fed a normal diet, but SBH/y exhibits spontaneously proteinuria,[150] whereas SBN/y is protected from proteinuria development.[151] After salt loading, salt-sensitive SBH/y animals develop hypertension in contrast to salt-resistant SBN/y rats;[151] the SBH/y strain is also more susceptible to develop glomerulosclerosis than SBN/y.[151] Moreover, Sabra rats exihbit also a sexual dimorphism of the renal phenotype, since the progression of proteinuria development and FSGS is more accelerated in males compared with females.[151]

Cosegregation and linkage analyses

Yagil *et al.*[150,152] performed in two (SBH/y $\times$ SBN/y) F2 crosses studied under low-salt diet and after Nx a total genome scan strategy to identify proteinuria QTL. The authors detected in male rats three QTLs linked to proteinura but not to BP on RNO2, RNO17 and RNO20 and in female rats three QTLs linked to proteinuria on RNO11, RNO13 and RNO20 (Tables 1 and 5).[150,152] Moreover, only in males three additional proteinuria QTLs on RNO3, RNO6 and RNO9 were identified at which, however, the SBH/y allele associated with lower albuminuria levels suggesting a protective effect of the SBH/y genome at these QTL (Tables 1 and 5).[150,152]

Consomic/congenic studies

Consomic studies on proteinuria development in the Sabra rat model were reported for the identified QTL on RNO2, RNO17 and RN20[150,151] and for two further chromosomes from previous studies, for example, RNO1 and RNOX, on which no proteinuria QTL was mapped by linkage analysis (Table 2).[153,154] In a first report, the transfer of RNO1 or RNO17 from SBH/y into the SBN/y background resulted in both consomic strains in marked proteinuria that was several-fold higher in male animals in response to Nx compared with male SBN/y Nx animals (Table 2).[150,151] These results confirm the role of genes on RNO1 and RNO17 for proteinuria development in male SBH/y rats (Table 3).[150,151] However, the extent of glomerulosclerosis was not considerably influenced by either chromosome.[151] In a more recent study, in which the reciprocal single-chromosome transfer from SBN/y into the SBH/y background was used, the functional evidence for the presence of a proteinuria-related QTL on chromosomes RNO1, RNO2 and RNO20 in both male and female rats was confirmed (Table 2).[150] In contrast, a significant effect on proteinuria of RNO17 was only detected in males and no effect in either sex was found for RNOX (Table 2).[150] Genome-wide gene expression analysis in kidneys from SBH/y and SBN/y with and without uninephrectomy revealed differentially expressed genes that mapped within the boundaries of the proteinuria-related QTLs identified in these strains. Overall 24 transcripts in males and 30 in females were identified, only 4 of which Tubb5 (Tubulin, beta 5 class I), Ubd (Ubiquitin D), Psmb8 (Proteasome (prosome, macropain) subunit, beta type 8 (Large multifunctional peptidase 7)) and C2 (Complement component 2) on RNO20 were common to both sexes (Table 3).[150]

SPONTANEOUSLY HYPERTENSIVE RAT

Strain breeding

Okamoto and Aoki[155] established the SHR model from outbred WKY rats by selective breeding for high BP under normal conditions in Kyoto, Japan. These not fully inbred stocks were imported by the

National Institutes of Health in the United States.[16,156] Subsequently, several colonies were established, which lack genetic homogeneity and thus show phenotypic variance.[16,156–158]

Strain characteristics

The SHR rat is a model that develops spontaneous hypertension in early life.[159] The salt sensitivity status of hypertension may vary between different colonies of SHR strains.[160,161] In addition, SHR rats develop several other phenotypes including insulin resistance,[162–165] renal damage such as mild proteinuria and albuminuria, glomerular sclerosis and pathological alterations in small vessels with age.[166,167]

Cosegregation and linkage analyses

Herring *et al.*[168] investigated whether the IgG/Fc-γ receptor pathway in glomeruli is capable of modulating hypertensive glomerular disease such as albuminuria in SHR. In an (SHR-A3 × SHR-B2)-F2 intercross, the authors identified in male SHR-A3 a QTL on RNO6 linked to *IgG* subclasses (Tables 1 and 5), which was derived from the *IgH* gene (immunoglobulin heavy chain complex).[168] Subsequently, single-nucleotide polymorphism genotyping revealed that allelic variation in the *IgH* haplotype block or neighboring genes may modify the susceptibility to hypertensive renal injury without a BP influence.[168]

Congenic studies

Renal transplant studies showed that the kidneys of BN are more susceptible to hypertension-induced damage compared with SHR.[169] St Lezin *et al.*[170] assumed that underlying genetic susceptibility factors, that is, the *Rf* loci on RNO1, which were originally identified in the FHH rat,[77,89,90] may contribute to renal failure in BN.[170] Subsequently, the authors introgressed a 22-cM segment of RNO1, which may overlap with *Rf-2*, *Bpfh-1* and possibly with *Rf-1* in FHH,[77,89,90] from normotensive BN/Cr rats into the hypertensive SHR/Ola background of the congenic strain SHR.BN-D1Mit3/Igf2 (Tables 2 and 3).[170] The results in these strains demonstrated that in BN rats susceptibility to renal damage such as proteinuria and glomerular injury in response to deoxycorticosterone acetate-salt loading was also significantly aggravated by one or more genes related to the transferred RNO1 segment, carrying *Rf* loci from FHH (Table 2).[170]

SPONTANEOUSLY HYPERTENSIVE RAT, STROKE-PRONE

Strain breeding

By Okamoto *et al.*[171] the A1-sb and A3 substrains of SHR were crossed to select offsprings for further inbreeding, when parents were highly susceptible to stroke.[172] The resulting inbred strain SHRSP/A3N was defined as SHRSP.[171]

Strain characteristics

SHRSP show salt-sensitive spontaneous hypertension, vascular and particularly cerebrovascular lesions associated with a high incidence of strokes.[160,171,173,174] In addition, SHRSP develop salt-induced renal damage such as albuminuria,[48] severe glomerulosclerosis, tubulo-insterstitial fibrosis, inflammation,[48,160] renal vascular lesions,[173] and an increase in the glomerular renin-angiotensin system.[175] Male SHRSP rats are more affected in developing renal lesions compared with females.[176]

Cosegregation and linkage analyses

In a genotype/phenotype cosegregation study in an SHRSP/SHR F2 intercross population including both genders, Gigante *et al.*[176] detected QTL regions on RNO1, RNO4, RNO10 and RNO16 affecting renal damage in this cross (Tables 1 and 5), while both susceptible and protective alleles of SHRSP were identified for renal changes such as the degree of renal vascular and parenchymal lesions.

Consomic studies

On RNO1 several QTLs linked to BP,[47,48,54,77,90,177–183] stroke or stroke-associated phenotypes,[182,184] and renal damages[48,54,77,90,141,142,151] could be identified in different rat models. To demonstrate genetic differences in the incidence of hypertension, cerebral stroke and renal damage under salt loading in tap water (1% NaCl), Ishikawa *et al.*[185] analysed five congenic rat strains, in which different chromosomal segments from WKY/Izm-RNO1 were transferred into the SHRSP/Izm background (Table 2). The findings showed that one or more gene(s) on RNO1 was/were associated with salt-induced renal damage, that is, albuminuria and glomerulosclerosis, which act independently of BP in SHRSP.

CONCLUSIONS

The increasing incidence and prevalence of complex forms of CKD in the general human population[1–5,9] poses a major global health problem. Understanding the molecular basis, including the genetic susceptibility, of complex CKD may therefore open new opportunities for early diagnosis and development of novel therapeutic strategies that protect against CKD, halt CKD or even reverse the apparently inevitable progressive course of CKD.[186] During the last two decades significant progress in our understanding of the development of kidney diseases has been achieved by unravelling the mechanisms underlying rare familial forms of human kidney diseases.[187] Notwithstanding this progress, knowledge about genetic factors that contribute to common forms of complex CKD is scarce, although human genome-wide association studies sought to close this gap by identifying susceptibility loci for CKD or reduced kidney function, that is, GFR.[99,188,189] So far susceptibility loci could be identified on all human chromosomes (HSA), 1–22, except the sex chromosomes.[2,3,8,99,188,190–201] Only a few studies, however, were successful, identifying within their associated genomic interval a single locus with a plausible candidate as a susceptibility locus for more common forms of CKD. Thus, a locus on chromosome 22 carrying a variant in the Apolipoprotein L-1 (*APOL1*) gene has been shown to explain a major portion of the increased genetic risk for non-diabetic CKD observed in African Americans.[198,202] Moreover, an identified missense variant in Cubilin (*CBN*) has been associated with albuminuria in the general population and in patients with diabetes.[203]

In the genetic mapping studies in inbred rat models only a few molecular variants have been clearly identified to date, including *Arp3* in the BUF rat[19] and *Rab38* in the FHH rat[104,105] (Table 3), although no variant has been ultimately confirmed, for example, by single gene congenic strains or further transgenic models. Nevertheless, given their phenotypic characteristics the panel of rat models summarized here represents an important tool in our armamentarium to explore the genetics of the most prevalent forms of complex CKD to which both arterial hypertension and type-2 diabetes mellitus are major contributors.[1–5,9] In this regard, this panel is a valuable experimental and data resource in which numerous QTLs associated with renal (disease) phenotypes have been identified on all rat chromosomes (Tables 4 and 5). Moreover, several important findings obtained from studies in these models have already contributed to our knowledge on the genetic determination of complex renal disease phenotypes. Hence, studies in the FHH,[90,93,95,97] MWF[141–143] and SS[53,54] rat

models highlighted the role of major susceptibility loci that in concert and genetic interaction with multiple other loci influence renal disease susceptibility (Table 5). Moreover, these models allow the combination of genetic analyses with unlimited gene expression studies,[65,70,150] including timed renal and compartment-specific expression analysis during the onset of renal disease phenotypes such as albuminuria,[143,204] while these experimental algorithms are difficult or impossible to pursue in humans due to the limited access to renal tissue. The comprehensive exploitation of the genotype–renal phenotype associations that are inherited in this panel of rat strains is therefore suitable for making a significant contribution to the development of an integrated approach to the systems genetics of CKD.[189] This may pave the way for the development of eagerly awaited novel and successful prognostic, diagnostic and therapeutic tools for the integrated management of common forms of CKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Fogarty DG, Rich SS, Hanna L, Warram JH, Krolewski AS. Urinary albumin excretion in families with type 2 diabetes is heritable and genetically correlated to blood pressure. *Kidney Int* 2000; **57**: 250–257.
2 Krolewski AS, Poznik GD, Placha G, Canani L, Dunn J, Walker W, Smiles A, Krolewski B, Fogarty DG, Moczulski D, Araki S, Makita Y, Ng DP, Rogus J, Duggirala R, Rich SS, Warram JH. A genome-wide linkage scan for genes controlling variation in urinary albumin excretion in type II diabetes. *Kidney Int* 2006; **69**: 129–136.
3 Freedman BI, Bowden DW, Rich SS, Xu J, Wagenknecht LE, Ziegler J, Hicks PJ, Langefeld CD. Genome-wide linkage scans for renal function and albuminuria in Type 2 diabetes mellitus: the Diabetes Heart Study. *Diabet Med* 2008; **25**: 268–276.
4 Mottl AK, Vupputuri S, Cole SA, Almasy L, Goring HH, Diego VP, Laston S, Shara N, Lee ET, Best LG, Fabsitz RR, MacCluer JW, Umans JG, North KE. Linkage analysis of albuminuria. *J Am Soc Nephrol* 2009; **20**: 1597–1606.
5 Divers J, Freedman BI. Susceptibility genes in common complex kidney disease. *Curr Opin Nephrol Hypertens* 2010; **19**: 79–84.
6 Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–2047.
7 de Jong PE, van der Velde M, Gansevoort RT, Zoccali C. Screening for chronic kidney disease: where does Europe go? *Clin J Am Soc Nephrol* 2008; **3**: 616–623.
8 Chambers JC, Zhang W, Lord GM, van der Harst P, Lawlor DA, Sehmi JS, Gale DP, Wass MN, Ahmadi KR, Bakker SJ, Beckmann J, Bilo HJ, Bochud M, Brown MJ, Caulfield MJ, Connell JM, Cook HT, Cotlarciuc I, Davey SG, de Silva R, Deng G, Devuyst O, Dikkeschei LD, Dimkovic N, Dockrell M, Dominiczak A, Ebrahim S, Eggermann T, Farrall M, Ferrucci L, Floege J, Forouhi NG, Gansevoort RT, Han X, Hedblad B, Homan van der Heide JJ, Hepkema BG, Hernandez-Fuentes M, Hypponen E, Johnson T, de Jong PE, Kleefstra N, Lagou V, Lapsley M, Li Y, Loos RJ, Luan J, Luttropp K, Marechal C, Melander O, Munroe PB, Nordfors L, Parsa A, Peltonen L, Penninx BW, Perucha E, Pouta A, Prokopenko I, Roderick PJ, Ruokonen A, Samani NJ, Sanna S, Schalling M, Schlessinger D, Schlieper G, Seelen MA, Shuldiner AR, Sjogren M, Smit JH, Snieder H, Soranzo N, Spector TD, Stenvinkel P, Sternberg MJ, Swaminathan R, Tanaka T, Ubink-Veltmaat LJ, Uda M, Vollenweider P, Wallace C, Waterworth D, Zerres K, Waeber G, Wareham NJ, Maxwell PH, McCarthy MI, Jarvelin MR, Mooser V, Abecasis GR, Lightstone L, Scott J, Navis G, Elliott P, Kooner JS. Genetic loci influencing kidney function and chronic kidney disease. *Nat Genet* 2010; **42**: 373–375.
9 James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. *Lancet* 2010; **375**: 1296–1309.
10 Gansevoort RT, Nauta FL, Bakker SJ. Albuminuria: all you need to predict outcomes in chronic kidney disease? *Curr Opin Nephrol Hypertens* 2010; **19**: 513–518.
11 Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–2081.
12 Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, Zanchetti A. Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 2001; **12**: 218–225.
13 Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106**: 1777–1782.
14 Toto RD. Proteinuria reduction: mandatory consideration or option when selecting an antihypertensive agent? *Curr Hypertens Rep* 2005; **7**: 374–378.
15 Ritz E. Renal dysfunction as a novel risk factor: microalbuminuria and cardiovascular risk. *Kidney Int Suppl* 2005; **January**: S25–S28.
16 Rapp JP. Genetic analysis of inherited hypertension in the rat. *Physiol Rev* 2000; **80**: 135–172.
17 Cowley Jr AW, Liang M, Roman RJ, Greene AS, Jacob HJ. Consomic rat model systems for physiological genomics. *Acta Physiol Scand* 2004; **181**: 585–592.
18 Yamada S, Masuko K, Ito M, Nagayo T. Spontaneous thyoma in Buffalo rats. *Gann* 1973; **64**: 287–291.
19 Akiyama K, Morita H, Suetsugu S, Kuraba S, Numata Y, Yamamoto Y, Inui K, Ideura T, Wakisaka N, Nakano K, Oniki H, Takenawa T, Matsuyama M, Yoshimura A. Actin - related protein 3 (Arp3) is mutated in proteinuric BUF/Mna rats. *Mamm Genome* 2008; **19**: 41–50.
20 Matsuyama M, Amo H. Host origin of lymphoid cells in thymomas developed from subcutaneous thymus grafts in Buffalo rats. *Gann* 1977; **68**: 293–300.
21 Matsuyama M, Yamada C, Hiai H. A single dominant susceptible gene determines spontaneous development of thymoma in BUF/Mna rat. *Jpn J Cancer Res* 1986; **77**: 1066–1068.
22 Nakamura T, Oite T, Shimizu F, Matsuyama M, Kazama T, Koda Y, Arakawa M. Sclerotic lesions in the glomeruli of Buffalo/Mna rats. *Nephron* 1986; **43**: 50–55.
23 Kato F, Watanabe M. Biochemical study on spontaneous thymoma rats with motor dysfunction. *J Pharmacobiodyn* 1983; **6**: 275–279.
24 Murayama S, Yagyu S, Higo K, Ye C, Mizuno T, Oyabu A, Ito M, Morita H, Maeda K, Serikawa T, Matsuyama M. A genetic locus susceptible to the overt proteinuria in BUF/Mna rat. *Mamm Genome* 1998; **9**: 886–888.
25 Le Berre L, Herve C, Buzelin F, Usal C, Soulillou JP, Dantal J. Renal macrophage activation and Th2 polarization precedes the development of nephrotic syndrome in Buffalo/Mna rats. *Kidney Int* 2005; **68**: 2079–2090.
26 van Goor H, van der Horst ML, Atmosoerodjo J, Joles JA, van Tol A, Grond J. Renal apolipoproteins in nephrotic rats. *Am J Pathol* 1993; **142**: 1804–1812.
27 Matsuyama M, Yamada C, Kojima A. Possible single dosage effects of the nude gene: suppression of spontaneous development of thymoma and nephropathy in BUF/Mna-rnu/+ rats. *Jpn J Cancer Res* 1987; **78**: 40–44.
28 Howie AJ, Kizaki T, Beaman M, Morland CM, Birtwistle RJ, Adu D, Michael J, Williams AJ, Walls J, Matsuyama M. Different types of segmental sclerosing glomerular lesions in six experimental models of proteinuria. *J Pathol* 1989; **157**: 141–151.
29 Matsuyama M, Ogiu T, Kontani K, Yamada C, Kawai M, Hiai H, Nakamura T, Shimizu F, Toyokawa T, Kinoshita Y. Genetic regulation of the development of glomerular sclerotic lesions in the BUF/Mna rat. *Nephron* 1990; **54**: 334–337.
30 Matsuyama M, Suzuki H, Yamada S, Ito M, Nagayo T. Ultrastructure of spontaneous and urethan-induced thymomas in buffalo rats. *Cancer Res* 1975; **35**: 2771–2779.
31 Taguchi O, Kontani K, Ikeda H, Matsuyama M. An intrinsic thymic epithelial abnormality is responsible for the spontaneous development of predominantly lymphocytic thymomas in BUF/Mna rats. *Jpn J Cancer Res* 1992; **83**: 1166–1171.
32 Nakamura T, Matsuyama M, Kojima A, Ogiu T, Kubota A, Suzuki Y, Arakawa M, Shimizu F. The effect of thymectomy on the development of nephropathy in spontaneous thymoma rats of the BUF/Mna strain. *Clin Exp Immunol* 1988; **71**: 350–352.
33 Toyokawa T, Hato F, Mizoguchi S, Kimura S, Matsuyama M, Kinoshita Y. Remarkable changes in mitogen responsiveness and rosette-forming capacity of thymocytes with aging due to possible disorders of thymic hormone secretion from thymus epithelial cells of spontaneous thymoma Buffalo/Mna rats. *Cell Mol Biol* 1987; **33**: 363–374.
34 Matsuyama M, Amo H, Yamada C. [Spontaneous thymoma occurring in Buffalo/Mna rats]. *Jikken Dobutsu* 1981; **30**: 67–71.
35 Amo H, Saito M, Nagao S, Yagiu S, Takahashi H, Morita H, Morita TM, Matsuyama M. Genetic regulation of slowly progressing mild muscle atrophy in fast-twitch muscles of BUF/Mna rats. *Muscle Nerve* 1997; **20**: 1258–1263.
36 Dahl LK, Heine M, Tassinari L. Effects of chronia excess salt ingestion. Evidence that genetic factors play an important role in susceptibility to experimental hypertension. *J Exp Med* 1962; **115**: 1173–1190.
37 Iwai J. Dahl salt-sensitive and salt-resistant rats. *Hypertension* 1987; **9**(Suppl. I): I-18–I-20.
38 Kurtz TW, Morris Jr. RC. Hypertension in the recently weaned Dahl salt-sensitive rat despite a diet deficient in sodium chloride. *Science* 1985; **230**: 808–810.
39 Jaffe D, Sutherland LE, Barker DM, Dahl LK. Effects of chronic excess salt ingestion. Morphologic findings in kidneys of rats with differing genetic susceptibilities to hypertension. *Arch Pathol* 1970; **90**: 1–16.
40 Sustarsic DL, McPartland RP, Rapp JP. Developmental patterns of blood pressure and urinary protein, kallikrein, and prostaglandin E2 in Dahl salt-hypertension-susceptible rats. *J Lab Clin Med* 1981; **98**: 599–606.
41 Raij L, Azar S, Keane W. Mesangial immune injury, hypertension, and progressive glomerular damage in Dahl rats. *Kidney Int* 1984; **26**: 137–143.
42 Khan NJ, Hampton JA, Lacher DA, Rapp JP, Gohara AF, Goldblatt PJ. Morphometric evaluation of the renal arterial system of Dahl salt-sensitive and salt-resistant rats on a high salt diet. I. Interlobar and arcuate arteries. *Lab Invest* 1987; **57**: 714–723.
43 Sterzel RB, Luft FC, Gao Y, Schnermann J, Briggs JP, Ganten D, Waldherr R, Schnabel E, Kriz W. Renal disease and the development of hypertension in salt-sensitive Dahl rats. *Kidney Int* 1988; **33**: 1119–1129.

44 Hampton JA, Bernardo DA, Khan NA, Lacher DA, Rapp JP, Gohara AF, Goldblatt PJ. Morphometric evaluation of the renal arterial system of Dahl salt-sensitive and salt-resistant rats on a high salt diet. II. Interlobular arteries and intralobular arterioles. *Lab Invest* 1989; **60**: 839–846.
45 Karlsen FM, Andersen CB, Leyssac PP, Holstein-Rathlou NH. Dynamic Autoregulation and Renal Injury in Dahl Rats. *Hypertension* 1997; **30**: 975–983.
46 Herrera VM, Didishvili T, Lopez LV, Zander K, Traverse S, Gantz D, Herscovitz H, Ruiz-Opazo N. Hypertension exacerbates coronary artery disease in transgenic hyperlipidemic Dahl salt-sensitive hypertensive rats. *Mol Med* 2001; **7**: 831–844.
47 Siegel A, Planert M, Rademacher S, Poyan Mehr A, Kossmehl P, Wehland M, Stoll M, Kreutz R. Genetic loci contribute to the progression of vascular and cardiac hypertrophy in salt-sensitive spontaneous hypertension. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1211–1217.
48 Siegel AK, Kossmehl P, Planert M, Schulz A, Wehland M, Stoll M, Bruijn JA, de Heer E, Kreutz R. Genetic linkage of albuminuria and renal injury in Dahl salt-sensitive rats on a high-salt diet: comparison with spontaneously hypertensive rats. *Physiol Genomics* 2004; **18**: 218–225.
49 Wendt N, Schulz A, Siegel AK, Weiss J, Wehland M, Sietmann A, Kossmehl P, Grimm D, Stoll M, Kreutz R. Rat chromosome 19 transfer from SHR ameliorates hypertension, salt-sensitivity, cardiovascular and renal organ damage in salt-sensitive Dahl rats. *J Hypertens* 2007; **25**: 95–102.
50 Koop K, Eikmans M, Wehland M, Baelde H, Ijpelaar D, Kreutz R, Kawachi H, Kerjaschki D, de Heer E, Bruijn JA. Selective loss of podoplanin protein expression accompanies proteinuria and precedes alterations in podocyte morphology in a spontaneous proteinuric rat model. *Am J Pathol* 2008; **173**: 315–326.
51 Wendt N, Schulz A, Qadri F, Bolbrinker J, Kossmehl P, Winkler K, Stoll M Vetter R, Kreutz R. Genetic analysis of salt-sensitive hypertension in Dahl rats reveals a link between cardiac fibrosis and high cholesterol. *Cardiovasc Res* 2009; **81**: 618–626.
52 Packard M, Saad Y, Gunning WT, Gupta S, Shapiro J, Garrett MR. Investigating the effect of genetic background on proteinuria and renal injury using two hypertensive strains. *Am J Physiol Renal Physiol* 2009; **296**: F839–F846.
53 Poyan MA, Siegel AK, Kossmehl P, Schulz A, Plehm R, de Bruijn JA, de Heer E, Kreutz R. Early onset albuminuria in Dahl rats is a polygenetic trait that is independent from salt loading. *Physiol Genomics* 2003; **14**: 209–216.
54 Garrett MR, Dene H, Rapp JP. Time-course genetic analysis of albuminuria in Dahl salt-sensitive rats on low-salt diet. *J Am Soc Nephrol* 2003; **14**: 1175–1187.
55 Mattson DL, Kunert MP, Kaldunski ML, Greene AS, Roman RJ, Jacob HJ, Cowley Jr. AW. Influence of diet and genetics on hypertension and renal disease in Dahl salt-sensitive rats. *Physiol Genomics* 2004; **16**: 194–203.
56 Mattson DL, Meister CJ, Marcelle ML. Dietary protein source determines the degree of hypertension and renal disease in the Dahl salt-sensitive rat. *Hypertension* 2005; **45**: 736–741.
57 Inoko M, Kihara Y, Morii I, Fujiwara H, Sasayama S. Transition from compensatory hypertrophy to dilated, failing left ventricles in Dahl salt-sensitive rats. *Am J Physiol* 1994; **267**: H2471–H2482.
58 Ogihara T, Asano T, Ando K, Sakoda H, Anai M, Shojima N, Ono H, Onishi Y, Fujishiro M, Abe M, Fukushima Y, Kikuchi M, Fujita T. High-salt diet enhances insulin signaling and induces insulin resistance in Dahl salt-sensitive rats. *Hypertension* 2002; **40**: 83–89.
59 Ogihara T, Asano T, Fujita T. Contribution of salt intake to insulin resistance associated with hypertension. *Life Sci* 2003; **73**: 509–523.
60 Shehata MF. Important genetic checkpoints for insulin resistance in salt-sensitive (S) Dahl rats. *Cardiovasc Diabetol* 2008; **7**: 19.
61 Garrett MR, Joe B, Yerga-Woolwine S. Genetic linkage of urinary albumin excretion in Dahl salt-sensitive rats: influence of dietary salt and confirmation using congenic strains. *Physiol Genomics* 2006; **25**: 39–49.
62 Moreno C, Dumas P, Kaldunski ML, Tonellato PJ, Greene AS, Roman RJ, Cheng Q, Wang Z, Jacob HJ, Cowley Jr. AW. Genomic map of cardiovascular phenotypes of hypertension in female Dahl S rats. *Physiol Genomics* 2003; **15**: 243–257.
63 Toland EJ, Yerga-Woolwine S, Farms P, Cicila GT, Saad Y, Joe B. Blood pressure and proteinuria effects of multiple quantitative trait loci on rat chromosome 9 that differentiate the spontaneously hypertensive rat from the Dahl salt-sensitive rat. *J Hypertens* 2008; **26**: 2134–2141.
64 Kumarasamy S, Gopalakrishnan K, Toland EJ, Yerga-Woolwine S, Farms P, Morgan EE, Joe B. Refined mapping of blood pressure quantitative trait loci using congenic strains developed from two genetically hypertensive rat models. *Hypertens Res* 2011; **34**: 1263–1270.
65 Garrett MR, Gunning WT, Radecki T, Richard A. Dissection of a genetic locus influencing renal function in the rat and its concordance with kidney disease loci on human chromosome 1q21. *Physiol Genomics* 2007; **30**: 322–334.
66 PhysGen. *Program for Genomic Applications (PGA): Physiogenomics of Stressors in Derived Consomic Rats [Online]*. Medical College of Wisconsin, PhysGen, Milwaukee, WI. http://pga.mcw.edu, 2005.
67 Schachter AD, Ichimura T, Kohane IS. Chromosomes 18 and X are quantitative trait loci for nephrotic-range proteinuria in rats. *Pediatr Nephrol* 2005; **20**: 1717–1723.
68 Mattson DL, Dwinell MR, Greene AS, Kwitek AE, Roman RJ, Jacob HJ, Cowley Jr. AW. Chromosome substitution reveals the genetic basis of Dahl salt-sensitive hypertension and renal disease. *Am J Physiol Renal Physiol* 2008; **295**: F837–F842.
69 Cowley Jr. AW, Roman RJ, Kaldunski ML, Dumas P, Dickhout JG, Greene AS, Jacob HJ. Brown Norway chromosome 13 confers protection from high salt to consomic Dahl S rat. *Hypertension* 2001; **37**(2 Part 2): 456–461.
70 Liang M, Yuan B, Rute E, Greene AS, Olivier M, Cowley Jr. AW. Insights into Dahl salt-sensitive hypertension revealed by temporal patterns of renal medullary gene expression. *Physiol Genomics* 2003; **12**: 229–237.
71 Liu Y, Taylor NE, Lu L, Usa K, Cowley Jr. AW, Ferreri NR, Yeo NC, Liang M. Renal medullary microRNAs in Dahl salt-sensitive rats: miR-29b regulates several collagens and related genes. *Hypertension* 2010; **55**: 974–982.
72 Lu L, Li P, Yang C, Kurth T, Misale M, Skelton M, Moreno C, Roman RJ, Greene AS, Jacob HJ, Lazar J, Liang M, Cowley Jr AW. Dynamic convergence and divergence of renal genomic and biological pathways in protection from Dahl salt-sensitive hypertension. *Physiol Genomics* 2010; **41**: 63–70.
73 Moreno C, Williams JM, Lu L, Liang M, Lazar J, Jacob HJ, Cowley Jr. AW, Roman RJ. Narrowing a region on rat chromosome 13 that protects against hypertension in Dahl SS-13BN congenic strains. *Am J Physiol Heart Circ Physiol* 2011; **300**: H1530–H1535.
74 Tschopp TB, Zucker MB. Hereditary defect in platelet function in rats. *Blood* 1972; **40**: 217–226.
75 Provoost AP, de Keijzer MH. The fawn-hooded rat: a model for chronic renal failure. In: Gretz N and Strauch M (eds) *Experimental and Genetic Rat Models of Chronic Renal Failure*. Karger, Basel, 1993, pp 100–114.
76 Verseput GH, Provoost AP, van Tol A, Koomans HA, Joles JA. Hyperlipidemia is secondary to proteinuria and is completely normalized by angiotensin-converting enzyme inhibition in hypertensive fawn-hooded rats. *Nephron* 1997; **77**: 346–352.
77 Brown DM, Provoost AP, Daly MJ, Lander ES, Jacob HJ. Renal disease susceptibility and hypertension are under independent genetic control in the fawn-hooded rat. *Nat Genet* 1996; **12**: 44–51.
78 van Dokkum RP, Jacob HJ, Provoost AP. Difference in susceptibility of developing renal damage in normotensive fawn-hooded (FHL) and August x Copenhagen Irish (ACI) rats after N(omega)-nitro-L-arginine methyl ester induced hypertension. *Am J Hypertens* 1997; **10**(10 Part 1): 1109–1116.
79 LaVail MM. Fawn-hooded rats, the fawn mutation and interaction of pink-eyed and red-eyed dilution genes. *J Hered* 1981; **72**: 286–287.
80 Prieur DJ, Meyers KM. Genetics of the fawn-hooded rat strain. The coat color dilution and platelet storage pool deficiency are pleiotropic effects of the autosomal recessive red-eyed dilution gene. *J Hered* 1984; **75**: 349–352.
81 Kuijpers MH, Provoost AP, de Jong W. Development of hypertension and proteinuria with age in fawn-hooded rats. *Clin Exp Pharmacol Physiol* 1986; **13**: 201–209.
82 Raymond SL, Dodds WJ. Characterization of the fawn-hooded rat as a model for hemostatic studies. *Thromb Diath Haemorrh* 1975; **33**: 361–369.
83 Kreisberg JI, Karnovsky MJ. Focal glomerular sclerosis in the fawn-hooded rat. *Am J Pathol* 1978; **92**: 637–652.
84 Kuijpers MH, Gruys E. Spontaneous hypertension and hypertensive renal disease in the fawn-hooded rat. *Br J Exp Pathol* 1984; **65**: 181–190.
85 Kuijpers MH, de Jong W. Relationship between blood pressure level, renal histopathological lesions and plasma renin activity in fawn-hooded rats. *Br J Exp Pathol* 1987; **68**: 179–187.
86 Kriz W, Hosser H, Hähnel B, Simons JL, Provoost AP. Development of vascular pole-associated glomerulosclerosis in the Fawn-hooded rat. *J Am Soc Nephrol* 1998; **9**: 381–396.
87 Kriz W, Hosser H, Hähnel B, Gretz N, Provoost AP. From segmental glomerulosclerosis to total nephron degeneration and interstitial fibrosis: a histopathological study in rat models and human glomerulopathies. *Nephrol Dial Transplant* 1998; **13**: 2781–2798.
88 Simons JL, Provoost AP, De Keijzer MH, Anderson S, Rennke HG, Brenner BM. Pathogenesis of glomerular injury in the fawn-hooded rat: effect of unilateral nephrectomy. *J Am Soc Nephrol* 1993; **4**: 1362–1370.
89 Brown DM, van Dokkum RP, Korte MR, McLauglin MG, Shiozawa M, Jacob HJ, Provoost AP. Genetic control of susceptibility for renal damage in hypertensive fawn-hooded rats. *Ren Fail* 1998; **20**: 407–411.
90 Shiozawa M, Provoost AP, van Dokkum RP, Majewski RR, Jacob HJ. Evidence of gene-gene interactions in the genetic susceptibility to renal impairment after unilateral nephrectomy. *J Am Soc Nephrol* 2000; **11**: 2068–2078.
91 Lopez B, Ryan RP, Moreno C, Sarkis A, Lazar J, Provoost AP, Jacob HJ, Roman RJ. Identification of a QTL on chromosome 1 for impaired autoregulation of RBF in fawn-hooded hypertensive rats. *Am J Physiol Renal Physiol* 2006; **290**: F1213–F1221.
92 Provoost AP, Shiozawa M, van Dokkum RP, Jacob HJ. Transfer of the Rf-1 region from FHH onto the ACI background increases susceptibility to renal impairment. *Physiol Genomics* 2002; **8**: 123–129.
93 Van Dijk SJ, Specht PA, Lutz MM, Lazar J, Jacob HJ, Provoost AP. Interaction between Rf-1 and Rf-4 quantitative trait loci increases susceptibility to renal damage in double congenic rats. *Kidney Int* 2005; **68**: 2462–2472.
94 Van Dijk SJ, Specht PA, Lazar J, Jacob HJ, Provoost AP. Renal damage susceptibility and autoregulation in RF-1 and RF-5 congenic rats. *Nephron Exp Nephrol* 2005; **101**: e59–e66.
95 Van Dijk SJ, Specht PA, Lazar J, Jacob HJ, Provoost AP. Synergistic QTL interactions between Rf-1 and Rf-3 increase renal damage susceptibility in double congenic rats. *Kidney Int* 2006; **69**: 1369–1376.
96 Van Dijk SJ, Specht PA, Lazar J, Jacob HJ, Provoost AP. Absence of an interaction between the Rf-1 and Rf-5 QTLs influencing susceptibility to renal damage in rats. *Nephron Exp Nephrol* 2006; **104**: e96–e102.
97 O'Meara CC, Lazar J, Hoffman M, Moreno C, Jacob HJ. Refined mapping of the renal failure RF-3 quantitative trait locus. *J Am Soc Nephrol* 2011; **22**: 518–525.

98 O'Meara CC, Lutz MM, Sarkis AB, Xu H, Kothinti RK, Hoffman M, Moreno C, Tabatabai NM, Lazar J, Roman RJ, Jacob HJ. A 4.1-Mb congenic region of Rf-4 contributes to glomerular permeability. *J Am Soc Nephrol* 2012; **23**: 825–833.
99 Köttgen A, Glazer NL, Dehghan A, Hwang SJ, Katz R, Li M, Yang Q, Gudnason V, Launer LJ, Harris TB, Smith AV, Arking DE, Astor BC, Boerwinkle E, Ehret GB, Ruczinski I, Scharpf RB, Chen YD, de Boer IH, Haritunians T, Lumley T, Sarnak M, Siscovick D, Benjamin EJ, Levy D, Upadhyay A, Aulchenko YS, Hofman A, Rivadeneira F, Uitterlinden AG, van Duijn CM, Chasman DI, Pare G, Ridker PM, Kao WH, Witteman JC, Coresh J, Shlipak MG, Fox CS. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 2009; **41**: 712–717.
100 Meyer TE, Verwoert GC, Hwang SJ, Glazer NL, Smith AV, van Rooij FJ, Ehret GB, Boerwinkle E, Felix JF, Leak TS, Harris TB, Yang Q, Dehghan A, Aspelund T, Katz R, Homuth G, Kocher T, Rettig R, Ried JS, Gieger C, Prucha H, Pfeufer A, Meitinger T, Coresh J, Hofman A, Sarnak MJ, Chen YD, Uitterlinden AG, Chakravarti A, Psaty BM, van Duijn CM, Kao WH, Witteman JC, Gudnason V, Siscovick DS, Fox CS, Kottgen A. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six Loci influencing serum magnesium levels. *PLoS Genet* 2010; **6**: e1001045.
101 Mattson DL, Kunert MP, Roman RJ, Jacob HJ, Cowley Jr. AW. Substitution of chromosome 1 ameliorates L-NAME hypertension and renal disease in the fawn-hooded hypertensive rat. *Am J Physiol Renal Physiol* 2005; **288**: F1015–F1022.
102 Mattson DL, Dwinell MR, Greene AS, Kwitek AE, Roman RJ, Cowley Jr AW, Jacob HJ. Chromosomal mapping of the genetic basis of hypertension and renal disease in FHH rats. *Am J Physiol Renal Physiol* 2007; **293**: F1905–F1914.
103 Williams JM, Burke M, Lazar J, Jacob HJ, Roman RJ. Temporal characterization of the development of renal injury in FHH rats and FHH.1BN congenic strains. *Am J Physiol Renal Physiol* 2011; **300**: F330–F338.
104 Rangel-Filho A, Sharma M, Datta YH, Moreno C, Roman RJ, Iwamoto Y, Provoost AP, Lazar J, Jacob HJ. RF-2 gene modulates proteinuria and albuminuria independently of changes in glomerular permeability in the fawn-hooded hypertensive rat. *J Am Soc Nephrol* 2005; **16**: 852–856.
105 Oiso N, Riddle SR, Serikawa T, Kuramoto T, Spritz RA. The rat Ruby (R) locus is Rab38: identical mutations in Fawn-hooded and Tester-Moriyama rats derived from an ancestral Long Evans rat sub-strain. *Mamm Genome* 2004; **15**: 307–314.
106 Goto Y, Kakizaki M, Masaki N. Spontaneous diabetes produced by selective breeding of normal Wistar rats. *Proc Jpn Acad* 1975; **51**: 80–85.
107 Goto Y, Kakizaki M, Masaki N. The spontaneous diabetes rat: a model of noninsulin dependent diabetes mellitus. *Proc Jpn Acad* 1981; **57(ser.B)**: 381–384.
108 Portha B, Serradas P, Bailbe D, Suzuki K, Goto Y, Giroix MH. Beta-cell insensitivity to glucose in the GK rat, a spontaneous nonobese model for type II diabetes. *Diabetes* 1991; **40**: 486–491.
109 Östenson CG. The Goto-Kakizaki rat. In Sima AAF and Shafrir E eds. *Animal Models of Diabetes*. Harwood Academic Publishers, Amsterdam, 2001, pp. 197–211.
110 Portha B. Programmed disorders of beta-cell development and function as one cause for type 2 diabetes? The GK rat paradigm. *Diabetes Metab Res Rev* 2005; **21**: 495–504.
111 Ostenson CG, Khan A, Abdel-Halim SM, Guenifi A, Suzuki K, Goto Y, Efendic S. Abnormal insulin secretion and glucose metabolism in pancreatic islets from the spontaneously diabetic GK rat. *Diabetologia* 1993; **36**: 3–8.
112 Guenifi A, Abdel-Halim SM, Hoog A, Falkmer S, Ostenson CG. Preserved beta-cell density in the endocrine pancreas of young, spontaneously diabetic Goto-Kakizaki (GK) rats. *Pancreas* 1995; **10**: 148–153.
113 Phillips AO, Baboolal K, Riley S, Grone H, Janssen U, Steadman R, Williams J, Floege J. Association of prolonged hyperglycemia with glomerular hypertrophy and renal basement membrane thickening in the Goto Kakizaki model of non-insulin-dependent diabetes mellitus. *Am J Kidney Dis* 2001; **37**: 400–410.
114 Nobrega MA, Solberg Woods LC, Fleming S, Jacob HJ. Distinct genetic regulation of progression of diabetes and renal disease in the Goto-Kakizaki rat. *Physiol Genomics* 2009; **39**: 38–46.
115 Cheng ZJ, Vaskonen T, Tikkanen I, Nurminen K, Ruskoaho H, Vapaatalo H, Muller D, Park JK, Luft FC, Mervaala EM. Endothelial dysfunction and salt-sensitive hypertension in spontaneously diabetic Goto-Kakizaki rats. *Hypertension* 2001; **37**(2 Part 2): 433–439.
116 Yagihashi S, Goto Y, Kakizaki M, Kaseda N. Thickening of glomerular basement membrane in spontaneously diabetic rats. *Diabetologia* 1978; **15**: 309–312.
117 Sato N, Komatsu K, Kurumatani H. Late onset of diabetic nephropathy in spontaneously diabetic GK rats. *Am J Nephrol* 2003; **23**: 334–342.
118 Schrijvers BF, De Vriese AS, Van de Voorde J, Rasch R, Lameire NH, Flyvbjerg A. Long-term renal changes in the Goto-Kakizaki rat, a model of lean type 2 diabetes. *Nephrol Dial Transplant* 2004; **19**: 1092–1097.
119 Janssen U, Riley SG, Vassiliadou A, Floege J, Phillips AO. Hypertension superimposed on type II diabetes in Goto Kakizaki rats induces progressive nephropathy. *Kidney Int* 2003; **63**: 2162–2170.
120 Cao Y, Dubois DC, Sun H, Almon RR, Jusko WJ. Modeling diabetes disease progression and salsalate intervention in Goto-Kakizaki rats. *J Pharmacol Exp Ther* 2011; **339**: 896–904.
121 Shahni R, Gnudi L, King A, Jones P, Malik AN. Elevated levels of renal and circulating Nop-7-associated 2 (NSA2) in rat and mouse models of diabetes, in mesangial cells *in vitro* and in patients with diabetic nephropathy. *Diabetologia* 2011; **55**: 825–834.
122 Sassard J, Vincent M, Orea V, Privat P, Bataillard A. Genetics of blood pressure and associated phenotypes in the Lyon rat. *Clin Exp Hypertens* 1997; **19**: 567–575.
123 Su DF, Cerutti C, Barres C, Vincent M, Sassard J. Blood pressure and baroreflex sensitivity in conscious hypertensive rats of Lyon strain. *Am J Physiol* 1986; **251**(6 Part 2): H1111–H1117.
124 Dubay C, Vincent M, Samani NJ, Hilbert P, Kaiser MA, Beressi JP, Kotelevtsev Y, Beckmann JS, Soubrier F, Sassard J. Genetic determinants of diastolic and pulse pressure map to different loci in Lyon hypertensive rats. *Nat Genet* 1993; **3**: 354–357.
125 Vincent M, Cartier R, Privat P, Benzoni D, Samani NJ, Sassard J. Major cardiovascular risk factors in Lyon hypertensive rats. A correlation analysis in a segregating population. *J Hypertens* 1996; **14**: 469–474.
126 Bilusic M, Bataillard A, Tschannen MR, Gao L, Barreto NE, Vincent M, Wang T, Jacob HJ, Sassard J, Kwitek AE. Mapping the genetic determinants of hypertension, metabolic diseases, and related phenotypes in the lyon hypertensive rat. *Hypertension* 2004; **44**: 695–701.
127 Gilibert S, Bataillard A, Nussberger J, Sassard J, Kwitek AE. Implication of chromosome 13 on hypertension and associated disorders in Lyon hypertensive rats. *J Hypertens* 2009; **27**: 1186–1193.
128 Hackbarth H, Gärtner K, Alt JM, Stolte H. A subline of the Munich Wistar (MW) strain, response to selection for surface glomeruli. *Rat News Lett* 1980; **7**: 23.
129 Hackbarth H, Buttner D, Jarck D, Pothmann M, Messow C, Gartner K. Distribution of glomeruli in the renal cortex of Munich Wistar Fromter (MWF) rats. *Ren Physiol* 1983; **6**: 63–71.
130 Kreutz R, Kovacevic L, Schulz A, Rothermund L, Ketteler M, Paul M. Effect of high NaCl diet on spontaneous hypertension in a genetic rat model with reduced nephron number. *J Hypertens* 2000; **18**: 777–782.
131 Alt JM, Hackbarth H, Deerberg F, Stolte H. Proteinuria in rats in relation to age-dependent renal changes. *Lab Anim* 1980; **14**: 95–101.
132 Rovira-Halbach G, Alt JM, Brunkhorst R, Frei U, Kuhn K, Stolte H. Single nephron hyperfiltration and proteinuria in a newly selected rat strain with superficial glomeruli. *Ren Physiol* 1986; **9**: 317–325.
133 Remuzzi A, Puntorieri S, Mazzoleni A, Remuzzi G. Sex related differences in glomerular ultrafiltration and proteinuria in Munich-Wistar rats. *Kidney Int* 1988; **34**: 481–486.
134 Kaufmann K, Hackbarth H. Quantitative vergleichende Untersuchungen zur Bestimmung der Nierenkörperchenanzahl bei der Munich-Wistar-Frömter-Ratte und der Wistar-cryptorchic-Ratte. *Dtsch Tierärztl Wschr* 1990; **97**: 302–304.
135 Fassi A, Sangalli F, Maffi R, Colombi F, Mohamed EI, Brenner BM, Remuzzi G, Remuzzi A. Progressive glomerular injury in the MWF rat is predicted by inborn nephron deficit. *J Am Soc Nephrol* 1998; **9**: 1399–1406.
136 Gschwend S, Pinto-Sietsma SJ, Buikema H, Pinto YM, van Gilst WH, Schulz A, de Zeeuw D, Kreutz R. Impaired coronary endothelial function in a rat model of spontaneous albuminuria. *Kidney Int* 2002; **62**: 181–191.
137 Macconi D, Bonomelli M, Benigni A, Plati T, Sangalli F, Longaretti L, Conti S, Kawachi H, Hill P, Remuzzi G, Remuzzi A. Pathophysiologic implications of reduced podocyte number in a rat model of progressive glomerular injury. *Am J Pathol* 2006; **168**: 42–54.
138 Schulz A, Weiss J, Schlesener M, Hänsch J, Wehland M, Wendt N, Kossmehl P, Sietmann A, Grimm D, Stoll M, Nyengaard JR, Kreutz R. Development of overt proteinuria in the Munich Wistar Fromter rat is suppressed by replacement of chromosome 6 in a consomic rat strain. *J Am Soc Nephrol* 2007; **18**: 113–121.
139 Schulz A, Hänsch J, Kuhn K, Schlesener M, Kossmehl P, Nyengaard JR, Wendt N, Huber M, Kreutz R. Nephron deficit is not required for progressive proteinuria development in the Munich Wistar Fromter rat. *Physiol Genomics* 2008; **35**: 30–35.
140 Schulz A, Schlesener M, Weiss J, Hänsch J, Wendt N, Kossmehl P, Grimm D, Vetter R, Kreutz R. Protective effect of female gender on the development of albuminuria in a polygenetic rat model is enhanced further by replacement of a major autosomal QTL. *Clin Sci (Lond)* 2008; **114**: 305–311.
141 Schulz A, Litfin A, Kossmehl P, Kreutz R. Genetic dissection of increased urinary albumin excretion in the munich wistar fromter rat. *J Am Soc Nephrol* 2002; **13**: 2706–2714.
142 Schulz A, Standke D, Kovacevic L, Mostler M, Kossmehl P, Stoll M, Kreutz R. A major gene locus links early onset albuminuria with renal interstitial fibrosis in the MWF rat with polygenetic albuminuria. *J Am Soc Nephrol* 2003; **14**: 3081–3089.
143 van Es N, Schulz A, Ijpelaar D, van der Wal A, Kuhn K, Schütten S, Kossmehl P, Nyengaard JR, de Heer E, Kreutz R. Elimination of severe albuminuria in aging hypertensive rats by exchange of 2 chromosomes in double-consomic rats. *Hypertension* 2011; **58**: 219–224.
144 Schulz A, Schütten-Faber S, van Es N, Unland J, Schulte L, Kossmehl P, de Heer E, Kreutz R. Induction of albuminuria and kidney damage in SHR by transfer of chromosome 8 from Munich Wistar Fromter rats. *Physiol Genomics* 2011; **44**: 110–116.
145 Schulz A, Schütten S, Schulte L, Kossmehl P, Nyengaard JR, Vetter R, Huber M, Kreutz R. Genetic locus on MWF rat chromosome 6 affects kidney damage in response to L-NAME treatment in spontaneously hypertensive rats. *Physiol Genomics* 2010; **42**: 126–133.
146 Ben-Ishay D, Saliternik R, Welner A. Separation of two strains of rats with inbred dissimilar sensitivity to Doca-salt hypertension. *Experientia* 1972; **28**: 1321–1322.
147 Ben-Ishay D, Kobrin I, Saliternick-Vardi R, Feurstein G, Zamir N. The Sabra hypertension prone (H) and hypertension resistant (N) rat strain. *Paroi Arterielle* 1980; **6**: 157–159.
148 Yagil C, Katni G, Rubattu S, Stolpe C, Kreutz R, Lindpaintner K, Ganten D, Ben-Ishay D, Yagil Y. Development, genotype and phenotype of a new colony of the Sabra

hypertension prone (SBH/y) and resistant (SBN/y) rat model of slat sensitivity and resistance. *J Hypertens* 1996; **14**: 1175–1182.
149 Ben-Ishay D, Yagil Y. The Sabra hypertension-prone and -resistant strains. In: Ganten D and de Jong W (eds) *Experimental and Genetic Models of Hypertension*. Elsevier Science, Amsterdam, 1994, pp 272–299.
150 Yagil Y, Hessner M, Schulz H, Gosele C, Lebedev L, Barkalifa R, Sapojnikov M, Hubner N, Yagil C. Geno-transcriptomic dissection of proteinuria in the uninephrectomized rat uncovers a molecular complexity with sexual dimorphism. *Physiol Genomics* 2010; **42A**: 301–316.
151 Yagil C, Sapojnikov M, Katni G, Ilan Z, Zangen SW, Rosenmann E, Yagil Y. Proteinuria and glomerulosclerosis in the Sabra genetic rat model of salt susceptibility. *Physiol Genomics* 2002; **9**: 167–178.
152 Yagil C, Sapojnikov M, Wechsler A, Korol A, Yagil Y. Genetic dissection of proteinuria in the Sabra rat. *Physiol Genomics* 2006; **25**: 121–133.
153 Yagil C, Sapojnikov M, Kreutz R, Katni G, Lindpaintner K, Ganten D, Yagil Y. Salt susceptibility maps to chromosomes 1 and 17 with sex specificity in the Sabra rat model of hypertension. *Hypertension* 1998; **31**: 119–124.
154 Yagil C, Sapojnikov M, Kreutz R, Zurcher H, Ganten D, Yagil Y. Role of chromosome X in the Sabra rat model of salt-sensitive hypertension. *Hypertension* 1999; **33**(1 Part 2): 261–265.
155 Okamoto K, Aoki K. Development of a strain of spontaneously hypertensive rats. *Jpn Circ J* 1963; **27**: 282–293.
156 Nabika T, Nara Y, Ikeda K, Endo J, Yamori Y. Genetic heterogeneity of the spontaneously hypertensive rat. *Hypertension* 1991; **18**: 12–16.
157 Schedl HP, Wilson HD, Horst RL. Calcium transport and vitamin D in three breeds of spontaneously hypertensive rats. *Hypertension* 1988; **12**: 310–316.
158 Matsumoto K, Yamada T, Natori T, Ikeda K, Yamada J, Yamori Y. Genetic variability in SHR (SHRSR), SHRSP and WKY strains. *Clin Exp Hypertens A* 1991; **13**: 925–938.
159 Gray SD. Spontaneous hypertension in the neonatal rat. A review. *Clin Exp Hypertens A* 1984; **6**: 755–781.
160 Griffin KA, Churchill PC, Picken M, Webb RC, Kurtz TW, Bidani AK. Differential salt-sensitivity in the pathogenesis of renal damage in SHR and stroke prone SHR. *Am J Hypertens* 2001; **14**(4 Part 1): 311–320.
161 Rothermund L, Luckert S, Kossmehl P, Paul M, Kreutz R. Renal endothelin ET(A)/ET(B) receptor imbalance differentiates salt-sensitive from salt-resistant spontaneous hypertension. *Hypertension* 2001; **37**: 275–280.
162 Yamori Y, Ohtaka M, Ueshima H, Nara Y, Horie R, Shimamoto T, Komachi Y. Glucose tolerance in spontaneously hypertensive rats. *Jpn Circ J* 1978; **42**: 841–847.
163 Mondon CE, Reaven GM. Evidence of abnormalities of insulin metabolism in rats with spontaneous hypertension. *Metabolism* 1988; **37**: 303–305.
164 Reaven GM, Chang H. Relationship between blood pressure, plasma insulin and triglyceride concentration, and insulin action in spontaneous hypertensive and Wistar-Kyoto rats. *Am J Hypertens* 1991; **4**(1 Part 1): 34–38.
165 Hulman S, Falkner B, Chen YQ. Insulin resistance in the spontaneously hypertensive rat. *Metabolism* 1991; **40**: 359–361.
166 Feld LG, Van Liew JB, Galaske RG, Boylan JW. Selectivity of renal injury and proteinuria in the spontaneously hypertensive rat. *Kidney Int* 1977; **12**: 332–343.
167 Feld LG, Cachero S, Van Liew JB, Zamlauski-Tucker M, Noble B. Enalapril and renal injury in spontaneously hypertensive rats. *Hypertension* 1990; **16**: 544–554.
168 Herring SM, Gokul N, Monita M, Bell R, Boerwinkle E, Wenderfer SE, Braun MC, Doris PA. Immunoglobulin locus associates with serum IgG levels and albuminuria. *J Am Soc Nephrol* 2011; **22**: 881–889.
169 Churchill PC, Churchill MC, Bidani AK, Griffin KA, Picken M, Pravenec M, Kren St V, Wang LE, Wang JM, Kurtz N. TW. Genetic susceptibility to hypertension-induced renal damage in the rat. Evidence based on kidney-specific genome transfer. *J Clin Invest* 1997; **100**: 1373–1382.
170 St Lezin E, Griffin KA, Picken M, Churchill MC, Churchill PC, Kurtz TW, Liu W, Wang N, Kren V, Zidek V, Pravenec M, Bidani AK. Genetic isolation of a chromosome 1 region affecting susceptibility to hypertension-induced renal damage in the spontaneously hypertensive rat. *Hypertension* 1999; **34**: 187–191.
171 Okamoto K, Yamori Y, Nagaoka A. Establishment of the stroke-prone spontaneously hypertensive rat (SHR). *Circ Res* 1974; **34–35**(Suppl 1): 143–153.
172 Yamori Y. Importance of genetic factors in stroke: an evidence obtained by selective breeding of stroke-prone and -resistant SHR. *Jpn Circ J* 1974; **38**: 1095–1100.
173 Volpe M, Camargo MJ, Mueller FB, Campbell Jr. WG, Sealey JE, Pecker MS, Sosa RE, Laragh JH. Relation of plasma renin to end organ damage and to protection of K+ feeding in stroke-prone hypertensive rats. *Hypertension* 1990; **15**: 318–326.
174 Shimamura T, Nakajima M, Iwasaki T, Hayasaki Y, Yonetani Y, Iwaki K. Analysis of circadian blood pressure rhythm and target-organ damage in stroke-prone spontaneously hypertensive rats. *J Hypertens* 1999; **17**: 211–220.
175 Obata J, Nakamura T, Takano H, Naito A, Kimura H, Yoshida Y, Shimizu F, Guo DF, Inagami T. Increased gene expression of components of the renin-angiotensin system in glomeruli of genetically hypertensive rats. *J Hypertens* 2000; **18**: 1247–1255.
176 Gigante B, Rubattu S, Stanzione R, Lombardi A, Baldi A, Baldi F, Volpe M. Contribution of genetic factors to renal lesions in the stroke-prone spontaneously hypertensive rat. *Hypertension* 2003; **42**: 702–706.
177 Lindpaintner K, Hilbert P, Ganten D, Nadal-Ginard B, Inagami T, Iwai N. Molecular genetics of the SA-gene: cosegregation with hypertension and mapping to rat chromosome 1. *J Hypertens* 1993; **11**: 19–23.
178 Nara Y, Nabika T, Ikeda K, Sawamura M, Mano M, Endo J, Yamori Y. Basal high blood pressure cosegregates with the loci on chromosome 1 in the F2 generation from crosses between normotensive Wistar Kyoto rats and stroke-prone spontaneously hypertensive rats. *Biochem Biophys Res Commun* 1993; **194**: 1344–1351.
179 Gu L, Dene H, Deng AY, Hoebee B, Bihoreau MT, James M, Rapp JP. Genetic mapping of two blood pressure quantitative trait loci on rat chromosome 1. *J Clin Invest* 1996; **97**: 777–788.
180 Garrett MR, Dene H, Walder R, Zhang QY, Cicila GT, Assadnia S, Deng AY, Rapp JP. Genome scan and congenic strains for blood pressure QTL using Dahl salt-sensitive rats. *Genome Res* 1998; **8**: 711–723.
181 Hübner N, Lee YA, Lindpaintner K, Ganten D, Kreutz R. Congenic substitution mapping excludes Sa as a candidate gene locus for a blood pressure quantitative trait locus on rat chromosome 1. *Hypertension* 1999; **34**(4 Part 1): 643–648.
182 Kato N, Nabika T, Liang YQ, Mashimo T, Inomata H, Watanabe T, Yanai K, Yamori Y, Yazaki Y, Sasazuki T. Isolation of a chromosome 1 region affecting blood pressure and vascular disease traits in the stroke-prone rat model. *Hypertension* 2003; **42**: 1191–1197.
183 Kato N, Mashimo T, Nabika T, Cui ZH, Ikeda K, Yamori Y. Genome-wide searches for blood pressure quantitative trait loci in the stroke-prone spontaneously hypertensive rat of a Japanese colony. *J Hypertens* 2003; **21**: 295–303.
184 Rubattu S, Volpe M, Kreutz R, Ganten U, Ganten D, Lindpaintner K. Chromosomal mapping of quantitative trait loci contributing to stroke in a rat model of complex human disease. *Nat Genet* 1996; **13**: 429–434.
185 Ishikawa N, Harada Y, Maruyama R, Masuda J, Nabika T. Genetic effects of blood pressure quantitative trait loci on hypertension-related organ damage: evaluation using multiple congenic strains. *Hypertens Res* 2008; **31**: 1773–1779.
186 Pergola PE, Raskin P, Toto RD, Meyer CJ, Huff JW, Grossman EB, Krauth M, Ruiz S, Audhya P, Christ-Schmidt H, Wittes J, Warnock DG. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* 2011; **365**: 327–336.
187 D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med* 2011; **365**: 2398–2411.
188 Köttgen A, Pattaro C, Böger CA, Fuchsberger C, Olden M, Glazer NL, Parsa A, Gao X, Yang Q, Smith AV, O'Connell JR, Li M, Schmidt H, Tanaka T, Isaacs A, Ketkar S, Hwang SJ, Johnson AD, Dehghan A, Teumer A, Pare G, Atkinson EJ, Zeller T, Lohman K, Cornelis MC, Probst-Hensch NM, Kronenberg F, Tonjes A, Hayward C, Aspelund T, Eiriksdottir G, Launer LJ, Harris TB, Rampersaud E, Mitchell BD, Arking DE, Boerwinkle E, Struchalin M, Cavalieri M, Singleton A, Giallauria F, Metter J, de Boer IH, Haritunians T, Lumley T, Siscovick D, Psaty BM, Zillikens MC, Oostra BA, Feitosa M, Province M, de Andrade M, Turner ST, Schillert A, Ziegler A, Wild PS, Schnabel RB, Wilde S, Munzel TF, Leak TS, Illig T, Klopp N, Meisinger C, Wichmann HE, Koenig W, Zgaga L, Zemunik T, Kolcic I, Minelli C, Hu FB, Johansson A, Igl W, Zaboli G, Wild SH, Wright AF, Campbell H, Ellinghaus D, Schreiber S, Aulchenko YS, Felix JF, Rivadeneira F, Uitterlinden AG, Hofman A, Imboden M, Nitsch D, Brandstatter A, Kollerits B, Kedenko L, Magi R, Stumvoll M, Kovacs P, Boban M, Campbell S, Endlich K, Volzke H, Kroemer HK, Nauck M, Volker U, Polasek O, Vitart V, Badola S, Parker AN, Ridker PM, Kardia SL, Blankenberg S, Liu Y, Curhan GC, Franke A, Rochat T, Paulweber B, Prokopenko I, Wang W, Gudnason V, Shuldiner AR, Coresh J, Schmidt R, Ferrucci L, Shlipak MG, van Duijn CM, Borecki I, Kramer BK, Rudan I, Gyllensten U, Wilson JF, Witteman JC, Pramstaller PP, Rettig R, Hastie N, Chasman DI, Kao WH, Heid IM, Fox CS. New loci associated with kidney function and chronic kidney disease. *Nat Genet* 2010; **42**: 376–384.
189 Keller BJ, Martini S, Sedor JR, Kretzler M. A systems view of genetics in chronic kidney disease. *Kidney Int* 2012; **81**: 14–21.
190 Freedman BI, Beck SR, Rich SS, Heiss G, Lewis CE, Turner S, Province MA, Schwander KL, Arnett DK, Mellen BG. A genome-wide scan for urinary albumin excretion in hypertensive families. *Hypertension* 2003; **42**: 291–296.
191 Placha G, Canani LH, Warram JH, Krolewski AS. Evidence for different susceptibility genes for proteinuria and ESRD in type 2 diabetes. *Adv Chronic Kidney Dis* 2005; **12**: 155–169.
192 Fox CS, Yang Q, Guo CY, Cupples LA, Wilson PW, Levy D, Meigs JB. Genome-wide linkage analysis to urinary microalbuminuria in a community-based sample: the Framingham Heart Study. *Kidney Int* 2005; **67**: 70–74.
193 Hwang SJ, Yang Q, Meigs JB, Pearce EN, Fox CS. A genome-wide association for kidney function and endocrine-related traits in the NHLBI's Framingham Heart Study. *BMC Med Genet* 2007; **19**(8 Suppl 1): S10.
194 Iyengar SK, Abboud HE, Goddard KA, Saad MF, Adler SG, Arar NH, Bowden DW, Duggirala R, Elston RC, Hanson RL, Ipp E, Kao WH, Kimmel PL, Klag MJ Knowler WC, Meoni LA, Nelson RG, Nicholas SB, Pahl MV, Parekh RS, Quade SR, Rich SS, Rotter JI, Scavini M, Schelling JR, Sedor JR, Sehgal AR, Shah VO Smith MW, Taylor KD, Winkler CA, Zager PG, Freedman BI. Genome-wide scans for diabetic nephropathy and albuminuria in multiethnic populations: the family investigation of nephropathy and diabetes (FIND). *Diabetes* 2007; **56**: 1577–1585.
195 Leon JM, Freedman BI, Miller MB, North KE, Hunt SC, Eckfeldt JH, Lewis CE, Kraja AT, Djousse L, Arnett DK. Genome scan of glomerular filtration rate and albuminuria: the HyperGEN study. *Nephrol Dial Transplant* 2007; **22**: 763–771.
196 Kao WH, Klag MJ, Meoni LA, Reich D, Berthier-Schaad Y, Li M, Coresh J, Patterson N, Tandon A, Powe NR, Fink NE, Sadler JH, Weir MR, Abboud HE, Adler SG, Divers J, Iyengar SK, Freedman BI, Kimmel PL, Knowler WC, Kohn OF, Kramp K, Leehey DJ, Nicholas SB, Pahl MV, Schelling JR, Sedor JR, Thornley-Brown D, Winkler CA, Smith MW, Parekh RS. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet* 2008; **40**: 1185–1192.
197 Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, Oleksyk T, McKenzie LM, Kajiyama H, Ahuja TS, Berns JS, Briggs W, Cho ME, Dart RA, Kimmel PL, Korbet SM, Michel DM, Mokrzycki MH, Schelling JR, Simon E, Trachtman H,

Vlahov D, Winkler CA. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 2008; **40**: 1175–1184.
198 Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardy AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**: 841–845.
199 Behar DM, Rosset S, Tzur S, Selig S, Yudkovsky G, Bercovici S, Kopp JB, Winkler CA, Nelson GW, Wasser WG, Skorecki K. African ancestry allelic variation at the MYH9 gene contributes to increased susceptibility to non-diabetic end-stage kidney disease in Hispanic Americans. *Hum Mol Genet* 2010; **19**: 1816–1827.
200 Gudbjartsson DF, Holm H, Indridason OS, Thorleifsson G, Edvardsson V, Sulem P, de Vegt F, d'Ancona FC, den Heijer M, Wetzels JF, Franzson L, Rafnar T, Kristjansson K, Bjornsdottir US, Eyjolfsson GI, Kiemeney LA, Kong A, Palsson R, Thorsteinsdottir U, Stefansson K. Association of variants at UMOD with chronic kidney disease and kidney stones-role of age and comorbid diseases. *PLoS Genet* 2010; **6**: e1001039.
201 Böger CA, Heid IM. Chronic kidney disease: novel insights from genome-wide association studies. *Kidney Blood Press Res* 2011; **34**: 225–234.
202 Freedman BI, Kopp JB, Langefeld CD, Genovese G, Friedman DJ, Nelson GW, Winkler CA, Bowden DW, Pollak MR. The apolipoprotein L1 (APOL1) gene and nondiabetic nephropathy in African Americans. *J Am Soc Nephrol* 2010; **21**: 1422–1426.
203 Böger CA, Chen MH, Tin A, Olden M, Köttgen A, de Boer IH, Fuchsberger C, O'Seaghdha CM, Pattaro C, Teumer A, Liu CT, Glazer NL, Li M, O'Connell JR, Tanaka T, Peralta CA, Kutalik Z, Luan J, Zhao JH, Hwang SJ, Akylbekova E, Kramer H, van der Harst P, Smith AV, Lohman K, de Andrade M, Hayward C, Kollerits B, Tonjes A, Aspelund T, Ingelsson E, Eiriksdottir G, Launer LJ, Harris TB, Shuldiner AR, Mitchell BD, Arking DE, Franceschini N, Boerwinkle E, Egan J, Hernandez D, Reilly M, Townsend RR, Lumley T, Siscovick DS, Psaty BM, Kestenbaum B, Haritunians T, Bergmann S, Vollenweider P, Waeber G, Mooser V, Waterworth D, Johnson AD, Florez JC, Meigs JB, Lu X, Turner ST, Atkinson EJ, Leak TS, Aasarod K, Skorpen F, Syvanen AC, Illig T, Baumert J, Koenig W, Kramer BK, Devuyst O, Mychaleckyj JC, Minelli C, Bakker SJ, Kedenko L, Paulweber B, Coassin S, Endlich K, Kroemer HK, Biffar R, Stracke S, Volzke H, Stumvoll M, Magi R, Campbell H, Vitart V, Hastie ND, Gudnason V, Kardia SL, Liu Y, Polasek O, Curhan G, Kronenberg F, Prokopenko I, Rudan I, Arnlov J, Hallan S, Navis G, Parsa A, Ferrucci L, Coresh J, Shlipak MG, Bull SB, Paterson NJ, Wichmann HE, Wareham NJ, Loos RJ, Rotter JI, Pramstaller PP, Cupples LA, Beckmann JS, Yang Q, Heid IM, Rettig R, Dreisbach AW, Bochud M, Fox CS, Kao WH. CUBN is a gene locus for albuminuria. *J Am Soc Nephrol* 2011; **22**: 555–570.
204 Ijpelaar DH, Schulz A, Koop K, Schlesener M, Bruijn JA, Kerjaschki D, Kreutz R, de Heer E. Glomerular hypertrophy precedes albuminuria and segmental loss of podoplanin in podocytes in Munich-Wistar-Fromter rats. *Am J Physiol Renal Physiol* 2008; **294**: F758–F767.
205 Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat Genet* 1995; **11**: 241–247.
206 Le Berre L, Godfrin Y, Gunther E, Buzelin F, Perretto S, Smit H, Kerjaschki D, Usal C, Cuturi C, Soulillou JP, Dantal J. Extrarenal effects on the pathogenesis and relapse of idiopathic nephrotic syndrome in Buffalo/Mna rats. *J Clin Invest* 2002; **109**: 491–498.
207 Malek RL, Wang HY, Kwitek AE, Greene AS, Bhagabati N, Borchardt G, Cahill L, Currier T, Frank B, Fu X, Hasinoff M, Howe E, Letwin N, Luu TV, Saeed A, Sajadi H, Salzberg SL, Sultana R, Thiagarajan M, Tsai J, Veratti K, White J, Quackenbush J, Jacob HJ, Lee NH. Physiogenomic resources for rat models of heart, lung and blood disorders. *Nat Genet* 2006; **38**: 234–239.