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Supplementary Table 1. List of previously reported RCC GWAS loci

			Previously Reported GWAS				Current Study					
							Female			Male		
Locus	SNP	Neareast Gene	Study	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
1p32.3	rs4381241	*FAF1*	Scelo et al. (ref. 12)	1.11	1.07-1.15	3.1 x 10-10	1.17	1.08-1.27	4.0x10-4	1.15	1.06-1.24	9.3x10-5
2p21	rs7579899**	*EPAS1*	Purdue et al. (ref. 8)	1.15	1.10-1.21	2.3 x 10-9	1.08	0.99-1.16	0.11	1.19	1.12-1.26	1.4x10-6
2p21	rs11894252**	*EPAS1*	Purdue et al. (ref. 8)	1.14	1.09-1.20	1.8 x 10-8	1.09	1.01-1.18	0.08	1.19	1.12-1.26	9.3x10-7
2q22.3	rs12105918	*ZEB2*	Henrion et al. (ref. 10)	1.29	1.18-1.41	1.8 x 10-8	1.12	0.94-1.34	0.21	1.25	1.09-1.43	0.001
3p22.1	rs67311347		Scelo et al. (ref. 12)	0.9	0.87-0.94	2.5 x 10-8	0.86	0.78-0.95	0.005	0.89	0.82-0.96	0.006
3q26.2	rs10936602	*LRRIQ4*	Scelo et al. (ref. 12)	0.9	0.87-0.93	8.8 x 10-9	0.9	0.82-0.99	0.03	0.91	0.86-0.96	0.02
8p21.3	rs2241261	*RHOBTB2/TNFRSF10B*	Scelo et al. (ref. 12)	1.1	1.06-1.13	5.8 x 10-9	1.12	1.03-1.21	0.007	1.11	1.03-1.2	0.002
8q24	rs35252396*		Gudmundsson et al. (ref. 13)	1.27	1.18-1.37	5.4 x 10-11	1.17	1.08-1.26	3.0x10-4	1.09	1.03-1.16	0.01
10q24.33-q25.1	rs11813268	*OBFC1*	Scelo et al. (ref. 12)	1.12	1.07-1.17	3.9 x 10-8	1.11	0.99-1.25	0.06	1.13	1.02-1.25	0.007
11q13	rs7105934		Purdue et al. (ref. 8)	0.69	0.62-0.76	7.8 x 10-14	0.67	0.56-0.8	3.0x10-4	0.66	0.56-0.77	3.0x10-8
11q22.3	rs74911261	*KDELC2*	Scelo et al. (ref. 12)	1.41	1.27-1.57	2.1 x 10-10	1.34	0.99-1.8	0.05	1.46	1.13-1.88	0.005
11q22.3	rs1800057	*ATM*	Scelo et al. (ref. 12)	1.38	1.23-1.53	9.0 x 10-9	1.44	1.05-1.97	0.02	1.52	1.15-2.01	0.004
12p11.23	rs718314	*ITPR2*	Wu et al. (ref. 9)	1.19	1.13-1.26	8.9 x 10-10	1.14	1.03-1.26	0.004	1.25	1.18-1.33	1.6x10-9
12p11.23	rs1049380	*ITPR2*	Wu et al.(ref. 9)	1.18	1.12-1.25	6.1 x 10-9	1.18	1.07-1.30	4.0x10-4	1.27	1.17-1.37	7.0x10-10
12q24	rs4765623	*SCARB1*	Purdue et al. (ref. 8)	1.15	1.09-1.20	2.6 x 10-8	1.2	1.11-1.3	4.0x10-5	1.14	1.05-1.23	2.0x10-4
14q24.2	rs4903064	*DPF3*	Scelo et al. (ref. 12)	1.21	1.16-1.25	2.2 x 10-24	1.47	1.33-1.62	9.0x10-14	1.09	1.01-1.19	0.02

*Current study based on rs6470588, in complete LD with rs35252396.

**In complete linkage disequilibrium with sex-specific variant rs2121266 described the current study

Supplementary table 2

Details of the seventeen SNPs with sex-specific effects in the discovery GWAS

							Females (N=5,087)		Males (N=8,143)		
SNP	HGVS Nomenclature (GRCh37)	Nearest Gene	Position	Locus	FDR	SNP effect	MAF (Co/Ca)	P-value	MAF (Co/Ca)	P-value	P-interaction
rs4903064	NC_000014.8:g.73279420T>C	*DPF3*	Intron	14q24.2	<5%	CED	0.21/0.28	9.0x10-14	0.23/0.25	0.02	1.7x10-5
rs2121266	NC_000002.11:g.46535924C>A	*EPAS1*	Intron	2p21	<5%	SSE	0.39/0.40	0.2	0.39/0.42	2.5x10-7	0.04
rs12930199	NC_000016.9:g.6283321A>G	*RBFOX1*	Intron	16p13.3	<5%	SSE	0.31/0.36	4.0x10-7	0.33/0.33	0.38	7.2x10-4
rs10484683	NC_000006.11:g.148152077A>G	*SAMD5*	Intergenic	6q24.3	<5%	SSE	0.20/0.19	0.48	0.22/0.19	4.7x10-7	0.05
rs1548141	NC_000003.11:g.97942706C>A	*OR5H6*	Intron	3q11.2	<5%	SSE	0.50/0.50	0.5	0.49/0.52	4.8x10-7	0.003
rs78971134	NC_000012.11:g.107652531A>G	*BTBD11*	Intergenic	12q23.3	<5%	SSE	0.08/0.07	0.23	0.08/0.06	4.5x10-8	0.02
rs147304092	NC_000007.13:g.33442937A>G	*BBS9*	Intron	7p14.3	<30%	SSE	0.06/0.04	2.0x10-6	0.05/0.06	0.49	4.4x10-5
rs11744892	NC_000005.9:g.168519645C>T	*SLIT3*	Intergenic	5q35.1	<30%	SSE	0.32/0.36	2.0x10-6	0.34/0.34	0.63	4.2x10-4
rs2530551	NC_000007.13:g.34698321A>G	*NPSR1*	Intergenic	7p14.3	<30%	SSE	0.47/0.52	1.0x10-6	0.49/0.49	0.84	3.5x10-4
rs56960822	NC_000007.13:g.1363621C>T	*UNCX*	Intergenic	7p22.3	<30%	SSE	0.24/0.27	1.0x10-6	0.25/0.26	0.21	0.001
rs13027293	NC_000002.11:g.120001118G>T	*STEAP3*	Intron	2q14.2	<30%	SSE	0.34/0.37	8.0x10-6	0.36/0.35	0.28	5.3x10-5
rs6554676	NC_000005.9:g.1233350A>T	*SLC6A18*	Intron	5p15.33	<30%	CED	0.08/0.05	6.0x10-6	0.07/0.06	0.008	0.04
rs6583595	NC_000008.10:g.143249252T>C	*MIR4472-1*	Intergenic	8q24.3	<30%	SSE	0.20/0.19	0.56	0.20/0.17	7.0x10-6	0.006
rs4074759	NC_000008.10:g.143566504G>A	*BAI1*	Intron	8q24.3	<30%	SSE	0.17/0.17	0.57	0.18/0.15	8.0x10-6	0.02
rs7076813	NC_000010.10:g.121181167A>G	*GRK5*	Intron	10q26.11	<30%	SSE	0.24/0.23	0.76	0.22/0.25	6.0x10-6	0.003
rs12364512	NC_000011.9:g.133588934G>A	*SPATA19*	Intergenic	11q25	<30%	SSE	0.12/0.16	4.0x10-6	0.14/0.14	0.68	3.7x10-4
rs35121694	NC_000022.10:g.45626085G>A	*KIAA0930*	Intron	22q13.31	<30%	SSE	0.18/0.20	7.0x10-6	0.19/0.19	0.61	1.9x10-4

CED=Concordant Effect Direction
SSE= Single Sex Effect

Supplementary table 3

Association results of 17 SNPs from replication and joint meta-analysis

				Discovery					Replication					Combined						
				Female		Male			Female		Male			Female			Male			
				(N=5,087)		(N=8,143)			(N=2,974)		(N=8,113)			(N=8,061)			(N=16,256)			
SNP	Nearest Gene	Alleles		OR[95%CI]	P	OR[95%CI]	P	P-int	OR[95%CI]	P	OR[95%CI]	P	P-int	OR [95%CI]	Meta P-value	Het P-value	OR [95%CI]	Meta P-value	Het P-value	P-int
rs4903064	*DPF3*	C	T	1.47 [1.33-1.62]	9.0x10-14	1.09 [1.011-1.19]	0.02	1.7x10-5	1.24 [1.07-1.42]	0.003	1.09[0.98-1.21]	0.1	0.18	1.38[1.27-1.50]	1.5x10-14	0.1	1.09[1.03-1.16]	0.005	0.54	0.002
rs2121266	*EPAS1*	C	A	1.06 [0.97-1.15]	0.2	1.2 [1.12-1.28]	2.5x10-7	0.04	1.143 [1.00-1.30]	0.03	1.15 [1.05-1.26]	0.002	0.79	1.09 [1.01-1.17]	0.02	0.002	1.18 [1.12-1.25]	1.8x10-9	0.58	0.03
rs147304092	*BBS9*	G	A	0.62 [0.52-0.76]	2.0x10-6	1.05 [0.91-1.22]	0.49	4.4x10-5	0.97 [0.76-1.24]	0.81	1.2 [1.00-1.43]	0.04	0.12	0.72[0.63-0.84]	1.0x10-5	0.03	1.11[0.99-1.24]	0.08	0.54	0.008
rs13027293	*STEAP3*	T	G	1.23 [1.12-1.35]	8..0x10-6	0.96 [0.89-1.03]	0.28	5.3x10-5	0.87 [0.77-1.00]	0.04	1 [0.91-1.10]	0.95	0.16	1.10[1.02-1.19]	0.01	1.6x10-4	0.97[0.92-1.03]	0.37	0.52	9.8x10-7
rs6554676	*SLC6A18*	A	T	0.62 [0.51-0.77]	6.0x10-6	0.81 [0.69-0.95]	0.008	0.04	0.80 [0.61-1.05]	0.11	0.81 [0.67-0.99]	0.04	0.89	0.68 [0.58-0.81]	6.1x10-6	0.07	0.81 [0.72-92]	0.001	0.67	0.09
rs10484683	*SAMD5*	G	A	0.96 [0.87-1.07]	0.48	0.8 [0.74-0.88]	4.7x10-7	0.05	1.04 [0.89-1.21]	0.63	0.93 [0.82-1.04]	0.19	0.1	0.98[0.90-1.07]	0.68	2.9x10-4	0.83[0.78-0.89]	1.7x10-8	0.2	0.1
rs78971134	*BTBD11*	G	A	0.91 [0.78-1.06]	0.23	0.69 [0.61-0.79]	4.5x10-8	0.02	0.97 [0.78-1.20]	0.78	0.87 [0.74-1.03]	0.1	0.35	0.93[0.82-1.06]	0.26	0.21	0.75[0.68-0.83]	1.6x10-8	0.15	0.14
rs11744892	*SLIT3*	T	C	1.24 [1.14-1.37]	2.0x10-6	1.01 [0.94-1.09]	0.63	4.2x10-4	0.96 [0.84-1.09]	0.49	0.99 [0.90-1.09]	0.88	0.61	1.15[1.07-1.23]	1.9x10-4	0.003	1.00[0.95-1.06]	0.87	0.3	0.001
rs2530551	*NPSR1*	G	A	1.23 [1.13-1.34]	1.0x10-6	1 [0.94-1.08]	0.84	3.5x10-4	1.04 [0.92-1.18]	0.53	1.04 [0.95-1.14]	0.36	0.89	1.17[1.09-1.25]	1.1x10-5	0.02	1.01[0.96-1.07]	0.61	0.63	6.1x10-4
rs56960822	*UNCX*	T	C	1.34 [1.19-1.52]	1.0x10-6	1.06 [0.96-1.17]	0.21	0.001	1.01 [0.85-1.20]	0.89	1.02 [0.90-0.90]	0.79	0.79	1.22[1.11-1.35]	4.4x10-5	0.02	1.04[0.97-1.12]	0.27	0.25	0.007
rs12930199	*RBFOX1*	G	A	1.25 [1.15-1.37]	4.0x10-7	1.03 [0.96-1.11]	0.38	7.2x10-4	1.05 [0.92-1.19]	0.5	1.03 [0.94-1.14]	0.51	0.73	1.18[1.10-1.27]	4.8x10-6	0.17	1.03[0.97-1.09]	0.28	0.46	0.002
rs1548141	*OR5H6*	A	C	1.02 [0.95-1.12]	0.5	1.19 [1.11-1.28]	4.8x10-7	0.003	0.94 [0.83-1.06]	0.3	1.02 [0.93-0.93]	0.65	0.23	1.00[0.94-1.06]	0.93	0.55	1.13[1.07-1.19]	1.1x10-5	0.06	0.07
rs6583595	*MIR4472-1*	T	C	0.97 [0.87-1.08]	0.56	0.83 [0.75-0.89]	7.0x10-6	0.006	0.88 [0.76-1.02]	0.09	0.96 [0.86-1.08]	0.53	0.34	0.98[0.90-1.07]	0.64	0.26	1.13[1.06-1.20]	2.7x10-4	0.01	0.36
rs4074759	*BAI1*	A	G	0.96 [0.87-1.08]	0.57	0.81 [0.74-0.89]	8.0x10-6	0.02	1.09 [0.93-1.29]	0.27	1.01 [0.89-1.13]	0.9	0.49	1.00[0.91-1.09]	0.95	0.31	0.87[0.81-0.93]	1.1x10-4	0.03	0.11
rs7076813	*GRK5*	A	G	0.99 [0.89-1.09]	0.76	1.2 [1.11-1.3]	6.0x10-6	0.003	0.96 [0.83-1.10]	0.52	1.03 [0.93-1.15]	0.54	0.34	0.99[0.91-1.08]	0.85	0.92	0.89[0.84-0.95]	2.9x10-4	0.007	7.3x10-4
rs12364512	*SPATA19*	A	G	1.34 [1.19-1.53]	4.0x10-6	1.02 [0.92-1.13]	0.68	3.7x10-4	0.87 [0.73-1.05]	0.14	1 [0.88-1.15]	0.97	0.27	1.18[1.06-1.30]	0.002	5.0x10-4	1.01[0.94-1.10]	0.74	0.96	3.2x10-4
rs35121694	*KIAA0930*	A	G	1.3 [1.16-1.47]	7.0x10-6	0.97 [0.89-1.07]	0.61	1.9x10-4	0.9 [0.77-1.06]	0.21	1.1 [0.98-1.23]	0.12	0.06	1.15[1.05-1.26]	0.002	4.1x10-4	1.01[0.95-1.09]	0.7	0.07	1.9x10-5

OR[95%CI]= Odds Ratio 95% confidence interval

Meta P-Value= Meta analysis P-value

Het P-value= Heterogeneity P-value among studies

P-int= sex-interaction or sex-difference P-value

Supplementary Table 4

Differential gene expression between males and females in 279 normal and 574 kidney tumour tissues

	Normal Tissue			Tumour Tissue		
	Log Fold Change	P-Value	FDR adjusted P-value	Log Fold Change	P-Value	FDR adjusted P-value
DPF3	-0.01	0.13	0.28	-0.02	0.02	0.09
EPAS1	0.06	0.23	0.39	-0.03	0.32	0.42
*RBFOX1*****	0.01	0.19	0.36	-0.01	0.10	0.21
SAMD5	-0.01	0.84	0.84	-0.09	1x10-5	8.5x10-5
*OR5H6*****	0.00	0.67	0.74	0.004	0.41	0.50
BTBD11	-0.14	9.8x10-4	0.01	-0.01	0.17	0.29
BBS9	0.02	0.04	0.14	-0.004	0.63	0.67
SLIT3	-0.05	0.36	0.51	0.01	0.74	0.74
*NPSR1****	-0.02	0.04	0.14	0.003	0.58	0.66
UNCX	-0.02	0.03	0.14	0.01	0.04	0.14
STEAP3	-0.03	0.32	0.49	-0.01	0.07	0.17
SLC6A18	0.16	0.11	0.27	-0.03	0.31	0.42
MIR4472-1	NA	NA	NA	NA	NA	NA
BAI1	0.02	0.06	0.17	0.01	0.13	0.25
GRK5	-0.01	0.67	0.74	-0.05	0.02	0.09
*SPATA19*****	0.00	0.70	0.74	0.01	0.24	0.37
KIAA0930	-0.01	0.6	0.74	-0.03	0.05	0.14

*Transcript expressed in less than 10% samples in normal tissues

** Transcript expressed in less than 10% samples in both normal and tumour tissues

Supplementary Table 5: Results of sex-specific eQTL analysis of the 17 SNP-transcript pairs in Normal and Tumour kidney tissues

		Kidney Normal Tissue						Kidney Tumour Tissue					
		Female			Male			Female			Male		
SNP	Gene	Beta	P-Value	FDR	Beta	P-Value	FDR	Beta	P-Value	FDR	Beta	P-Value	FDR
rs4074759	*BAI1*	-0.01	0.75	0.91	-0.001	0.90	0.98	-0.01	0.67	0.91	-0.01	0.67	0.92
rs147304092	*BBS9*	0.01	0.69	0.91	-0.01	0.65	0.98	0.05	0.21	0.91	0.04	0.34	0.92
rs78971134	*BTBD11*	-0.03	0.77	0.91	0.02	0.78	0.98	0.17	0.14	0.91	0.06	0.59	0.92
rs4903064	*DPF3*	0.01	0.72	0.91	-0.02	0.16	0.98	0.06	1.2x10-6	2.6x10-5	0.03	2.0x10-4	0.004
rs2121266	*EPAS1*	-0.01	0.91	0.91	0.03	0.52	0.98	0.05	0.59	0.91	-0.03	0.69	0.92
rs7076813	*GRK5*	-0.07	0.13	0.91	0.01	0.83	0.98	0.02	0.27	0.91	0.01	0.43	0.92
rs35121694	*KIAA0930*	-0.04	0.46	0.91	0.02	0.69	0.98	0.05	0.35	0.91	0.00	0.98	0.98
rs6583595	*MIR4472*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs2530551	*NPSR1*	NA	NA	NA	NA	NA	NA	0.01	0.10	0.91	-0.01	0.34	0.92
rs1548141	*OR5H6*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs12930199	*RBFOX1*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs10484683	*SAMD5*	0.01	0.91	0.91	0.01	0.79	0.98	-0.03	0.44	0.91	0.02	0.41	0.92
rs6554676	*SLC6A18*	-0.08	0.76	0.91	-0.23	0.23	0.98	-0.01	0.90	0.95	-0.21	0.01	0.06
rs11744892	*SLIT3*	-0.05	0.45	0.91	-0.02	0.61	0.98	0.03	0.67	0.91	-0.01	0.84	0.92
rs12364512	*SPATA19*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs13027293	*STEAP3*	-0.04	0.44	0.91	0.01	0.72	0.98	-0.06	0.53	0.91	0.01	0.93	0.98
rs56960822	*UNCX*	-0.02	0.22	0.91	0.00	0.68	0.98	-0.02	0.20	0.91	-0.02	0.06	0.44

NA= transcript not available or expressed in less than 10% samples